UNIVERSIDAD POLITÉCNICA DE MADRID

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**Automated detection and classification of brain injury lesions
on structural magnetic resonance imaging**

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Departamento de Tecnología Fotónica y Bioingeniería
Grupo de Bioingeniería y Telemedicina
E.T.S.I. de Telecomunicación

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<"*Tened paciencia y tendréis ciencia*" – Baltasar Gracián>

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SUMMARY - English

Brain injury constitutes a serious social and health problem of increasing magnitude and of great diagnostic and therapeutic complexity. Its high incidence and survival rate, after the initial critical phases, makes it a prevalent problem that needs to be addressed. In particular, according to the World Health Organization (WHO), brain injury will be among the 10 most common causes of disability by 2020. Neurorehabilitation improves both cognitive and functional deficits and increases the autonomy of brain injury patients. The incorporation of new technologies to the neurorehabilitation tries to reach a new paradigm focused on designing intensive, personalized, monitored and evidence-based treatments. Since these four characteristics ensure the effectivity of treatments.

Contrary to most medical disciplines, it is not possible to link symptoms and cognitive disorder syndromes, to assist the therapist. Currently, neurorehabilitation treatments are planned considering the results obtained from a neuropsychological assessment battery, which evaluates the functional impairment of each cognitive function (memory, attention, executive functions, etc.).

The research line, on which this PhD falls under, aims to design and develop a cognitive profile based not only on the results obtained in the assessment battery, but also on theoretical information that includes both anatomical structures and functional relationships and anatomical information obtained from medical imaging studies, such as magnetic resonance. Therefore, the cognitive profile used to design these treatments integrates information personalized and evidence-based. Neuroimaging techniques represent an essential tool to identify lesions and generate this type of cognitive dysfunctional profiles.

Manual delineation of brain anatomical regions is the classical approach to identify brain anatomical regions. Manual approaches present several problems related to inconsistencies across different clinicians, time and repeatability. Automated delineation is done by registering brains to one another or to a template. However, when imaging studies contain lesions, there are several intensity abnormalities and location alterations that reduce the performance of most of the registration algorithms based on intensity parameters. Thus, specialists may have to manually interact with imaging studies to select landmarks (called singular points in this PhD) or identify regions of interest. These two solutions have the same inconvenient than manual approaches, mentioned before. Moreover, these registration algorithms do not allow large and distributed deformations. This type of deformations may also appear when a stroke or a traumatic brain injury (TBI) occur.

This PhD is focused on the design, development and implementation of a new methodology to automatically identify lesions in anatomical structures. This methodology integrates algorithms whose main objective is to generate objective and reproducible results. It is divided into four stages: pre-processing, singular points identification, registration and lesion detection.

Pre-processing stage. In this first stage, the aim is to standardize all input data in order to be able to draw valid conclusions from the results. Therefore, this stage has a direct impact on the final results. It consists of three steps: skull-stripping, spatial and intensity normalization.

Singular points identification. This stage aims to automatize the identification of anatomical points (singular points). It involves the manual identification of anatomical points by the clinician. This automatic identification allows to identify a greater number of points which results in more information; to remove the factor associated to inter-subject variability and thus, the results are reproducible and objective; and to eliminate the time spent on manual marking. This PhD proposed an algorithm to automatically identify singular points (descriptor) based on a multi-detector approach. This algorithm contains multi-parametric (spatial and intensity) information. This algorithm has been compared with other similar algorithms found on the state of the art.

Registration. The goal of this stage is to put in spatial correspondence two imaging studies of different subjects/patients. The algorithm proposed in this PhD is based on descriptors. Its main objective is to compute a vector field to introduce distributed deformations (changes in different imaging regions), as large as the deformation vector indicates. The proposed algorithm has been compared with other registration algorithms used on different neuroimaging applications which are used with control subjects. The obtained results are promising and they represent a new context for the automatic identification of anatomical structures.

Lesion identification. This final stage aims to identify those anatomical structures whose characteristics associated to spatial location and area or volume has been modified with respect to a normal state. A statistical study of the atlas to be used is performed to establish which are the statistical parameters associated to the normal state. The anatomical structures that may be identified depend on the selected anatomical structures identified on the atlas. The proposed methodology is independent from the selected atlas.

Overall, this PhD corroborates the investigated research hypotheses regarding the automatic identification of lesions based on structural medical imaging studies (resonance magnetic studies). Based on these foundations, new research fields to improve the automatic identification of lesions in brain injury can be proposed.

SUMMARY - Spanish

El daño cerebral adquirido (DCA) es un problema social y sanitario grave, de magnitud creciente y de una gran complejidad diagnóstica y terapéutica. Su elevada incidencia, junto con el aumento de la supervivencia de los pacientes, una vez superada la fase aguda, lo convierten también en un problema de alta prevalencia. En concreto, según la Organización Mundial de la Salud (OMS) el DCA estará entre las 10 causas más comunes de discapacidad en el año 2020. La neurorrehabilitación permite mejorar el déficit tanto cognitivo como funcional y aumentar la autonomía de las personas con DCA. Con la incorporación de nuevas soluciones tecnológicas al proceso de neurorrehabilitación se pretende alcanzar un nuevo paradigma donde se puedan diseñar tratamientos que sean intensivos, personalizados, monitorizados y basados en la evidencia. Ya que son estas cuatro características las que aseguran que los tratamientos son eficaces.

A diferencia de la mayor parte de las disciplinas médicas, no existen asociaciones de síntomas y signos de la alteración cognitiva que faciliten la orientación terapéutica. Actualmente, los tratamientos de neurorrehabilitación se diseñan en base a los resultados obtenidos en una batería de evaluación neuropsicológica que evalúa el nivel de afectación de cada una de las funciones cognitivas (memoria, atención, funciones ejecutivas, etc.).

La línea de investigación en la que se enmarca este trabajo de investigación pretende diseñar y desarrollar un perfil cognitivo basado no sólo en el resultado obtenido en esa batería de test, sino también en información teórica que engloba tanto estructuras anatómicas como relaciones funcionales e información anatómica obtenida de los estudios de imagen. De esta forma, el perfil cognitivo utilizado para diseñar los tratamientos integra información personalizada y basada en la evidencia. Las técnicas de neuroimagen representan una herramienta fundamental en la identificación de lesiones para la generación de estos perfiles cognitivos.

La aproximación clásica utilizada en la identificación de lesiones consiste en delinear manualmente regiones anatómicas cerebrales. Esta aproximación presenta diversos problemas relacionados con inconsistencias de criterio entre distintos clínicos, reproducibilidad y tiempo. Por tanto, la automatización de este procedimiento es fundamental para asegurar una extracción objetiva de información. La delineación automática de regiones anatómicas se realiza mediante el registro tanto contra atlas como contra otros estudios de imagen de distintos sujetos. Sin embargo, los cambios patológicos asociados al DCA están siempre asociados a anomalías de intensidad y/o cambios en la localización de las estructuras. Este hecho provoca que los algoritmos de registro tradicionales basados en intensidad no funcionen correctamente y requieran la intervención del clínico para seleccionar ciertos puntos (que en esta tesis hemos denominado puntos singulares). Además estos algoritmos tampoco permiten que se produzcan deformaciones grandes deslocalizadas. Hecho que también puede ocurrir ante la presencia de lesiones provocadas por un accidente cerebrovascular (ACV) o un traumatismo craneoencefálico (TCE).

Esta tesis se centra en el diseño, desarrollo e implementación de una metodología para la detección automática de estructuras lesionadas que integra algoritmos cuyo objetivo principal es generar resultados que puedan ser reproducibles y objetivos. Esta metodología se divide en cuatro etapas: pre-procesado, identificación de puntos singulares, registro y detección de lesiones.

Los trabajos y resultados alcanzados en esta tesis son los siguientes:

Pre-procesado. En esta primera etapa el objetivo es homogeneizar todos los datos de entrada con el objetivo de poder extraer conclusiones válidas de los resultados obtenidos. Esta etapa, por tanto, tiene un gran impacto en los resultados finales. Se compone de tres operaciones: eliminación del cráneo, normalización en intensidad y normalización espacial.

Identificación de puntos singulares. El objetivo de esta etapa es automatizar la identificación de puntos anatómicos (puntos singulares). Esta etapa equivale a la identificación manual de puntos anatómicos por parte del clínico, permitiendo: identificar un mayor número de puntos lo que se traduce en mayor información; eliminar el factor asociado a la variabilidad inter-sujeto, por tanto, los resultados son reproducibles y objetivos; y elimina el tiempo invertido en el marcado manual de puntos. Este trabajo de investigación propone un algoritmo de identificación de puntos singulares (descriptor) basado en una solución multi-detector y que contiene información multi-paramétrica: espacial y asociada a la intensidad. Este algoritmo ha sido contrastado con otros algoritmos similares encontrados en el estado del arte.

Registro. En esta etapa se pretenden poner en concordancia espacial dos estudios de imagen de sujetos/pacientes distintos. El algoritmo propuesto en este trabajo de investigación está basado en descriptores y su principal objetivo es el cálculo de un campo vectorial que permita introducir deformaciones deslocalizadas en la imagen (en distintas regiones de la imagen) y tan grandes como indique el vector de deformación asociado. El algoritmo propuesto ha sido comparado con otros algoritmos de registro utilizados en aplicaciones de neuroimagen que se utilizan con estudios de sujetos control. Los resultados obtenidos son prometedores y representan un nuevo contexto para la identificación automática de estructuras.

Identificación de lesiones. En esta última etapa se identifican aquellas estructuras cuyas características asociadas a la localización espacial y al área o volumen han sido modificadas con respecto a una situación de normalidad. Para ello se realiza un estudio estadístico del atlas que se vaya a utilizar y se establecen los parámetros estadísticos de normalidad asociados a la localización y al área. En función de las estructuras delineadas en el atlas, se podrán identificar más o menos estructuras anatómicas, siendo nuestra metodología independiente del atlas seleccionado.

En general, esta tesis doctoral corrobora las hipótesis de investigación postuladas relativas a la identificación automática de lesiones utilizando estudios de imagen médica estructural, concretamente estudios de resonancia magnética. Basándose en estos cimientos, se han abierto nuevos campos de investigación que contribuyan a la mejora en la detección de lesiones.

I Introduction

In which the clinical and technical context, related to brain injury and neuroimaging, and structure of this thesis are presented.

<"The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory" – Santiago Ramón y Cajal>

I.1. Context

I.1.1. Acquired brain injury and cognitive functions

I.1.1.1 Acquired brain injury

Acquired Brain Injury (ABI) (Brain Injury Association of America 2014) is defined as an injury to the brain, which is not hereditary, congenital, degenerative, or induced by birth trauma. It may result in a significant impairment of an individual's physical, cognitive and psychosocial functioning. An ABI includes all types of traumatic brain injuries (TBI) as well as brain injuries caused by stroke (ischemic or hemorrhagic) and brain tumors. However, the cause featuring the greater significant health, social and occupational impact is TBI, followed by stroke (Murray, Lopez 1997).

The World Health Organization (WHO) estimates that TBI and stroke will become the leading cause of disability and will constitute two of the five major health challenges with the greatest economic impact on health policies by 2030 (C.D. Mathers 2006). The annual incidence of TBI and stroke in North America and Europe is estimated at up to 500 and 400 per 100,000 people, respectively (Garcia-Altes et al. 2012, Tagliaferri et al. 2006).

By dealing with the causes of ABI according to their etiology (Fig. I.1-A), approximately 81 percent of the cases are of vascular origin, whereas 19% are of traumatic origin and 2.7% of patients are affected by both causes (Defensor del Pueblo 2006). The prevalence of TBI is higher in all age groups until the section from 35 to 44 years old. From that point then, the number of new stroke cases increases considerably in relation with new TBI cases (Fig. I.1-B)

Figure I. 1 A: Classification of ABI according to their etiology. **B:** ABI etiology according to age.

Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) (Sacco et al. 2013). Depending on the specific cause which origins the stroke it can be classified into (1) ischemic and (2) hemorrhagic, as shown in Fig. I.2. Ischemic stroke represents between 67% and 80%, ICH between 7% and 20% and SAH between 1% and 7% of the total stroke cases. Incidence and prevalence of stroke increase progressively with age. 75% of strokes occur in people aged over 65 years. The mortality of stroke over the first month of evolution is 20%. Stroke represents the most significant determinant of permanent disability in adults, the second cause of death in the population (the first in women), the second cause of dementia and the most common reason of neurological hospitalization, with almost 70% of neurology service admissions. It is a medical

emergency, where each minute counts, from the appearance of symptoms until the treatment is established. As time passes, fewer are the possibilities of recovering (Martínez-Vila et al. 2011).

Figure I. 2 Stroke classification

Ischemic stroke accounts for about 87% of all cases, according to the American Stroke Association (American Heart and Stroke Association 2014). It occurs when a clot or a mass clogs a blood vessel, cutting off the blood flow to brain cells. The underlying condition for this type of obstruction is the development of fatty deposits lining the vessel walls. This condition is called atherosclerosis. These fatty deposits can cause two types of obstruction:

- *Cerebral thrombosis*. It refers to a thrombus (blood clot) that develops at the clogged part of the vessel.
- *Cerebral embolism*. It refers generally to a blood clot that forms at another location in the circulatory system, usually the heart and large arteries of the upper chest and neck. A second important cause of embolism is an irregular heartbeat, known as atrial fibrillation. It creates conditions where clots can form in the heart, dislodge and travel to the brain.

The atherosclerotic plaque reduces blood flow in the internal carotid artery. If the plaque ruptures, tiny pieces of it and clotted blood can travel in the bloodstream to the brain. A foreign mass travelling through the bloodstream is called an embolus. If it lodges in a small artery, blood flow to part of the brain stops, as shown in Fig. I. 3-A.

Hemorrhagic stroke accounts for about 13% of stroke cases according to the American Stroke Association (American Heart and Stroke Association 2014). It results from a weakened vessel that ruptures and bleeds into the surrounding brain. The blood accumulates and compresses the surrounding brain tissue. The two types of hemorrhagic strokes are (1) intracerebral (within the brain) hemorrhage or (2) subarachnoid hemorrhage (Fig. I.3-B) (American Heart and Stroke Association 2014).

Hemorrhagic stroke occurs when a weakened blood vessel ruptures. Two types of weakened blood vessels usually cause hemorrhagic stroke:

- *Aneurysms*. It is a ballooning of a weakened region of a blood vessel. If left untreated, the aneurysm continues to weaken until it ruptures and bleeds into the brain.
- *Arteriovenous malformations (AVMs)*. It is a cluster of abnormally formed blood vessels. Any one of these vessels can rupture, also causing bleeding into the brain.

Figure I. 3 A: Ischemic stroke. B: Hemorrhagic stroke. Source: (American Heart and Stroke Association 2014).

Traumatic brain injury (TBI) is defined by the Brain Injury Association of America (BIAUSA) (Brain Injury Association of America 2014) as a brain impairment caused by an external force, with no degenerative or congenital nature, which may produce a decrease or alteration of consciousness and may induce changes in cognitive and functional abilities. TBI is the most common cause of death and disability in young people (Ghajar 2000).

One of the first consequences of TBI is loss of consciousness, the duration and the extent of this loss of consciousness are the most significant indicators of the TBI gravity (del Pueblo 2006). After the gradual recovery of consciousness and orientation, most of patients present a great diversity of sequelae on cognitive, emotional and social levels. The nature and gravity of these sequelae depend not only on extension and location of brain injury but also on personality and intelligence of each patient before the incident.

TBI can be classified according to etiology, pathophysiology, brain injury and level of awareness (García-Molina 2011), as shown in Fig. I. 4.

Figure I. 4 TBI classification

According to the **etiology**, TBI can be classified into *penetrating* and *no penetrating*. *Penetrating* head injury is a head injury in which the dura mater, the outer layer of the meninges, is breached. This type of injury can be caused by high-velocity projectiles or objects of lower velocity such as knives, or bone fragments from a skull fracture that are driven into the brain. Although penetrating injuries account for only a small percentage of all TBI, they are associated with a high mortality rate, and only a third of people with this type of injury survive long enough to arrive at a hospital (Blissitt 2006). *No penetrating* injury, also known as closed head injury, is a trauma in which the brain is injured as a result of a blow to the head, or a sudden, violent motion that causes the brain to knock against the skull, but no object penetrates the brain.

Concerning **pathophysiology**, it has to be taken into account that neurological damage does not all occur immediately at the moment of impact (*primary injury*) but it evolves afterwards (*secondary injury*). *Secondary brain injury* is the leading cause of inhospital deaths after traumatic brain injury. Most secondary brain injuries are caused by brain swelling, with an increase in intracranial pressure and a subsequent decrease in cerebral perfusion leading to ischemia (Ghajar 2000).

Attending the type of **brain injury**, TBI can be classified into *focal* (brain contusions, lacerations and haematomas) and *diffuse* (axonal injury and brain swelling). *Diffuse axonal injury* produces multifocal lesions as a result of mechanical forces during the impact. These forces generate axonal stretch, twist and break. The most common affected brain structures as a result of diffuse axonal injury are white matter, corpus callosum and midbrain (Arfanakis et al. 2002).

Regarding the **level of awareness**, TBI is graded as *mild*, *moderate*, or *severe* on the basis of the level of consciousness or Glasgow Coma Scale (GCS) score after resuscitation (see Table I.1). *Mild* traumatic brain injury (GCS 13–15) is in most cases a concussion and there is full neurological recovery, although many of these patients have short-term memory and concentration difficulties. In *moderate* traumatic brain injury (GCS 9–13) the patient is lethargic or stuporous, and in *severe* injury (GCS 3–8) the patient is comatose, unable to open his or her eyes or follow commands (Ghajar 2000).

Table I. 1 Glasgow coma scale

Glasgow coma scale					
Eye opening		Motor response		Verbal response	
Spontaneous	4	Obeys	6	Oriented	5
To speech	3	Localises	5	Confused	4
To pain	2	Withdraws	4	Inappropriate	3
None	1	Abnormal flexion	3	Incomprehensible	2
		Extensor response	2	None	1
		None	1		

1.1.1.2 Cognitive functions

As mentioned before, TBI affects the cognitive functioning directly. TBI patients suffer from any type of impairment in 90% of cases. In particular, around 30% of impairments are

cognitive, whereas physical impairments represent around 20% (del Pueblo 2006). 71% of patients are unable to perform one or more of the basic activities involved in daily life without some form of assistance and 45% of patients are not able to perform any activity even with aid, as shown in Fig. I. 5.

Figure I. 5 Classification of TBI patients according to the need of help.

Table I. 2 shows the percentage of each type of impairment associated with stroke and TBI. Most of these impairments are directly related to cognitive functions.

Table I. 2 Classification of impairments according to the etiology.

Type of impairment	Stroke (%)	TBI (%)
To move outside	85	83
To do housework	74	67
To use hands/arms	55	46
To move at home	51	37
To take care of yourself	50	39
To interact	38	44
To communicate	37	41
To acquire knowledge and develop tasks	36	45
To see	32	25
To hear	24	20

Cognitive function refers to mental abilities used to engage in different aspects of everyday life. (Teri, McCurry & Logsdon 1997). The main cognitive functions are: memory, language, attention and executive functions (Fig. I.6).

Figure I. 6 Classification of cognitive functions

Memory is conceptualized as a multi-component system specialized in encoding, storing and retrieving information (Baddeley 2004). Anatomically speaking, it is supported mainly by structures in the medial temporal and frontal lobes, but there are other cortical and subcortical structures also involved in memory (Cabeza, Nyberg 2000).

Language is related to verbal communication. It relies heavily on memory, but it also does on executive functions (Antonucci, Reilly 2008). Cortical areas involved in language are mainly located in the frontal and parietotemporal lobes (Ojemann 1991).

Attention is a brain neurocognitive state of preparing what precedes perception and action. This cognitive function selectively focuses our consciousness while filtering the constant flow of sensory information, selects competent parallel processing among stimuli and activates brain zones for ordering appropriate responses. It is a result of cortical and subcortical networks (Estévez-González, García-Sánchez & Junqué 1997).

Executive functions are responsible for controlling and monitoring other cognitive functions and for abstract thinking such as planning and making decisions (Krawczyk 2002). They are said to be typically located in frontal cortices (Stuss, Alexander 2000). However, there are other brain structures, as thalamus, which appear to be involved in this cognitive function (Van der Werf et al. 2003).

As mentioned above, cognitive functions are distributed among brain cortex, as shown in Fig.I.7. This figure represents Brodmann areas. These areas were originally defined and numbered by Korbinian Brodmann based on the cytoarchitectural organization of neurons observed (Brodmann, Garey 2007). Many of these areas have been closely correlated to diverse cortical functions. It is the most widely known and frequently cited cytoarchitectural organization of the human cortex.

Figure I. 7 Brodmann areas.

I.1.2. Neuroplasticity and Neurorehabilitation

Neurorehabilitation is a complex clinical process to restore, reduce and compensate the impact of disabling conditions, trying to improve the deficits caused by ABI in order to reduce the functional limitations and increase the individual's ability to function in everyday life (Institut Guttmann - Neurorehabilitation Hospital 2014). This is achieved by the plastic character of the nervous system, where the brain is able to reconfigure neural connections generating new ()and/or changing existing ones (Freitas et al. 2011).

I.1.2.1 Neuroplasticity

Neuroplasticity or plasticity is an intrinsic property of the nervous system and it represents evolution's invention to enable the nervous system to escape the restrictions of its own genome and adapt to environment pressures, physiologic changes and experiences (Pascual-Leone et al. 2005). According to this theory, thinking, learning and acting, actually change both the brain's physical structure (anatomy) and functional organization (physiology) from top to bottom (Acharya et al. 2012).

Brain function may be represented by distributed neuronal networks that can be scattered from the anatomical aspect, but linked from the functional view. The activity of all relevant neurons throughout the brain, organized in neuronal networks, provide a most energy efficient, spatially compact and precise nodes. In such networks, specific brain regions are conceptualized as operators that contribute a given computation independent of the input (Pascual-Leone, Hamilton 2001). Inputs shift depending on the integration of a region in a distributed neural network and the layered and reticular structure of the cortex with rich refferent loops provides the substrate for rapid modulation of the engaged network nodes (Pascual-Leone et al. 2005). The response of neuronal networks after a lesion is never only the result of the injury itself, but also the way in which the rest of the brain is able to generate the function after brain injury (Pascual Leone, Tormos Muñoz 2010)(Pascual Leone, Tormos Muñoz 2010)

Whereas the brain was conceptualized as a machine, at the very beginning of neuroscience, it could now be thought of more as clay, both malleable and vulnerable towards positive and negative influences. There are limits to how much the brain can change, reorganize and heal, but these limits are not as imposing as might be assumed. In fact, thanks to the power of neuroplasticity, people are fully recovering from massive strokes and head traumas (Acharya et al. 2012).

However, these changes harbor the danger that the evolving pattern of neural activation may in itself lead to abnormal behavior. Plasticity is the mechanism for development and learning, as much as a cause of pathology. Thus, there are two types of plasticity: positive and negative. If an organism can recover after an injury to normal levels of performance, that adaptiveness could be considered as an example of '*positive*' plasticity. An excessive level of neuronal growth leading to spasticity or tonic paralysis, or an excessive release of neurotransmitters in response to injury which could kill nerve cells have to be considered a '*negative*' plasticity (Draganski et al. 2006).

The significance of neuroplasticity for rehabilitation is that it provides a mechanism for understanding therapeutic interventions. Thus, it may be possible to develop more effective recovery protocols by simulating the effects of such interventions on physiological and anatomical plasticity in the injured brain (Nudo 2003).

Following a brain injury, significant improvement will continue for some years. The extent of recovery depends not only on the damaged area, the nature and severity of the injury and the amount of injured tissue, but also on the age, the rehabilitation programs and psychosocial and environmental factors. Therefore, changes in the neuronal activity may be able to establish new activity patterns maintaining the functionality even after a lesion. In other words, changes in the network activity may not generate any behavioral change or bring an improvement in behavior (Pascual Leone, Tormos Muñoz 2010).

Advances in noninvasive neuroimaging techniques have facilitated investigation of mechanisms mediating recovery and rehabilitation of injury and led to development of new clinical interventions (Levin 2006).

1.1.2.2 Neurorehabilitation

As mentioned above, the goal of rehabilitation is to increase the independence level of ABI patients. The rehabilitation team is an interdisciplinary team composed basically of neurologists, neuropsychiatrists, physiotherapists, occupational therapists, psychologists, neuropsychologists, speech therapists and the family of the patient (Selzer et al. 2006). This team will recommend a treatment plan for each individual. In order for the neurorehabilitation to be effective and high quality, it must be (Institut Guttmann - Neurorehabilitation Hospital 2014):

- *Holistic*. It should take into account physical, cognitive, psychological, social and cultural dimensions of the personality, stage of progress and lifestyle of both the patient and his/her family.
- *Patient-oriented*. Customized health care strategies should be developed, focused on the patient and his/her family.

- *Inclusive.* Care plans should be designed and implemented by multidisciplinary teams made up of motivated practitioners being highly qualified and trained in multidisciplinary work.
- *Participatory.* The patient and his/her family's active cooperation is a must. It takes delivering right information and the patient and his/her family trusting the multidisciplinary team.
- *Sparing.* Treatment must aim at empowering the patient for maximum possible independence, trying to keep down frailty and technical aids dependency to a minimum.
- *Lifelong.* The patient's various needs throughout his/her life must be catered for by ensuring continuity of care from injury onset to eventual complications later in time.
- *Resolving.* Treatment has to include adequate human and material resources for efficiently resolving each patient's problems as per case.
- *Community-focused.* It is necessary to look for the solutions best adapted to the specific characteristics of the community and to further the creation of community resources favoring the best possible community reintegration of the disabled person.

The period of rehabilitation can be divided into different stages according to the gravity of the injury, as shown in Fig I.8.

Figure I. 8 Rehabilitation stages. (ICU: intensive care unit)

Critical and *acute* phases are the nearest phases to the injury event. Usually the patient is hospitalized in intensive care units, neurology or neurosurgery service. During these phases, there is a significant risk where serious complications may appear. The goal is the clinical stabilization, treatment and prevention of complications. In particular, within the critical phase, brain injuries are active and in evolution. Critical patients are stable from hemodynamic and respiratory points of view. However, they have a greater likelihood of developing complications from the lesion. Acute patients are stable from neurological perspective and they are at low-moderate risk of serious complications resulting from brain injury. These patients make progress in the functional, cognitive and behavioral rehabilitation.

In the *sub-acute* phase, the patient is stable and brain lesions begin to improve. Sub-acute patient is moved to a neurorehabilitation unit or to his/her home, where the patient not only requires health and nursing care, but also interdisciplinary and intensive rehabilitation. The main goal of this phase is to achieve the highest level of personal autonomy. This is the last stage where the patient needs to be hospitalized.

In the post-acute phase, the patient lives at her/his home and their relatives assume health care. The goal is the reintegration into the labor market, their original families and in society.

I.1.3. Medical imaging on brain injury

At the beginning of the 21st century, known as “the century of the brain”, it became clear that a breakthrough in understanding and repairing the brain could only be achieved by combining knowledge from various scientific disciplines (neurobiology, physics, cognitive psychology, computer sciences, engineering). This multidisciplinary tools will enable us to utilize modern theoretical and experimental tools in order to investigate the different structural and functional levels of the brain (Safra, Safra 2011). From 2002 to 2013, the European Union have funded 226 brain research projects (European Union 2015). Nowadays, there are two important international projects: (1) The International Initiative for Traumatic Brain Injury Research (InTBIR) (European Union 2015) and (2) Human Brain Project (HBP) (Human Brain Project 2015).

InTBIR (European Union 2015) is a collaborative effort of the European Commission (EC), the Canadian Institutes of Health Research (CIHR) and the National Institutes of Health (NIH), to advance clinical TBI research, treatment and care. It was set up in October 2011 and it will finish around 2020. The three specific objectives of this initiative are: (1) further establishing and promoting the use of harmonized, international standards for TBI clinical data collection; InTBIR supports the use of the TBI Common Data Elements (CDE) as standards for data collection; (2) creating a TBI patient registry by building common databases and linking them through an accessible, user-friendly interface for both entry and data search and (3) developing and applying sophisticated analytical tools to enable Comparative Effectiveness Research (CER) for TBI and identify best practices in early diagnosis and treatment.

The HBP (Human Brain Project 2015) will develop six ICT platforms, dedicated respectively to Neuroinformatics, Brain Simulation, High Performance Computing, Medical Informatics, Neuromorphic Computing and Neurorobotics. Over the course of the 10-year project (it was established in 2013), HBP researchers will simulate the human brain, develop brain-inspired computing technologies, map brain diseases, perform targeted mapping of the mouse and human brain, develop six Information and Communications Technology (ICT) platforms, drive translation of research into products and services and implement programs of education and knowledge management. All these efforts will be made in the context of a responsible research and innovation (RRI) strategy.

As a conclusion, it can be highlighted that brain research is one of the most important challenges of this century. Nowadays, there is still much to know about brain, so there is a great need to design and develop new technologies and to improve the existing ones. One of the most interesting areas regarding in vivo visualization of the brain is medical imaging technologies.

Medical imaging technologies have revolutionized the study of the brain by allowing doctors and researchers to look at the brain noninvasively. These diagnostic techniques, also known as neuroimaging techniques, have allowed for the first time the noninvasive evaluation of brain structure, allowing clinicians to infer causes of abnormal function due to different diseases (Hess, Purcell). In particular, prior to neuroimaging clinicians could only make

assumptions about the pathology and possible anatomical locations underlying the impairments being treated. Neuroimaging techniques allow the rehabilitation clinician to directly view most forms of gross anatomical neuropathology and assess brain integrity with a number of quantitative and qualitative methods (Schiff 2006, Seitz, Donnan 2010, Suskauer, Huisman 2009).

Medical imaging studies are critical to both the diagnosis and management of brain injury, though they may also come to play an important role in rehabilitation after brain injury (Stinear, Ward 2013). Due to understanding the brain systems that underlie the cognitive changes associated with brain injuries should help determine what to target in the rehabilitation of an individual with brain injury (Chen, D'Esposito 2010).

In order to understand the role of medical imaging in brain injury, it has to be taken into account that brain injury encompasses a heterogeneous group of intracranial injuries and includes both impairments at the time of the impact and a secondary cascade of damages requiring optimal medical and surgical management (Kim, Gean 2011).

Brain medical imaging, also known as neuroimaging, is divided into structural and functional. On the one hand, structural imaging techniques are used to visualize anatomical abnormalities and are commonly used to predict the outcome. Structural imaging techniques in patients include X-ray, computed tomography (CT) and magnetic resonance imaging (MRI). On the other hand, functional imaging techniques are used to measure haemodynamic or metabolic changes in the brain. Single photon emission computed tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) are the most common functional techniques (Metting et al. 2007). As the main objective in this Thesis is to analyze structural medical imaging, this section focuses on the use of CT and MRI on brain injury.

CT and MRI modalities play an important role in brain injury diagnosis and management. As shown in Fig. I.9, the major difference between CT and MRI is the different meaning of each grey intensity level. Fig. I. 10 shows a comparative among the CT and different MRI and their corresponding tissue meaning (Tushar 2013).

Figure I. 9 Differences between CT and MRI. T1w: T1 weighted MRI, T2w: T2 weighted MRI, FLAIR: Fluid-attenuated inversion recovery. Source: Radiology, St. Paul's hospital, The Catholic University of Korea - Seoul/KR

Gradation of intensity	CT	T1w MRI	T2w MRI	Flair T2 MRI
CSF	CSF	Cartilage	CSF
Edema	Edema	Fat	Cartilage
WM	GM	WM	WM
GM	WM	GM	WM
Blood	Cartilage	Edema	GM
Bone	Fat	CSF	Edema

Figure I. 10 Differences among different medical imaging studios according to gradation of intensity. WM: white matter, GM: gray matter, CSF: cerebrospinal fluid. (Tushar 2013)

In case of MRI modality, there are several acquisition sequences use to identify different types of brain lesions based mainly in different relaxation times. As the main difference among tissues is different relaxation times, as shown in Fig. I. 11.

Figure I. 11 Relationship between relaxation times and different types of tissues. The image in the left is a T1w MRI. The image in the right is a T2w MRI. (Pooley 2005)

Previous works have concluded that pathological changes on anatomical structures are always associated with intensity abnormalities and/or location alterations (Joel Ramirez, Fu Quiang Gao, Sandra E. Black 2008). Table I. 3 summarizes the types of change which take place in the different imaging modalities through different stages. As it can be seen, all the intensity changes imply either a hypointensity or a hyperintensity (Jitendra L Ashtekar, L Gill Naul 2014).

Table I. 3 Intensity changes associate with lesions on different imaging (Jitendra L Ashtekar, L Gill Naul 2014)

Stage	Time	CT	T1w MRI	T2w MRI
Hyperacute	<≈8 hours	hyperintense	Iso – to hypointense	Hyperintense
Acute	≈8-72 hours	hyperintense	Iso – to hypointense	Hypointense
Early acute	≈3-7 days	hyperintense	hyperintense	Hypointense
Late subacute	≈1 week - months	isodense	hyperintense	Hyperintense
Chronic	months - years	hypointense	hypointense	Hypointense

The answer to which imaging modality is better for visualizing the brain is dependent on the purpose of the examination. CT and MRI are complementary techniques, each one with its own strengths and weaknesses (see Table I. 4). Choosing the appropriate examination depends

on (1) the time of imaging acquisition, (2) the part of the head being examined and (2) the age of the patient, among other considerations (Hess, Purcell).

Table I. 4 CT vs MRI, main advantages.

Advantages	
CT	MRI
Much faster than MRI, making it the study of choice in cases of emergencies.	No use of ionizing radiation
Less cost than MRI, it is sufficient to exclude many neurological disorders.	Much greater range of available soft tissue contrast.
Less sensitive to patient motion during the examination.	It is more sensitive and specific for abnormalities within the brain itself.
Easier to perform in claustrophobic or very heavy patients.	Can be performed in any imaging plane without having to physically move the patient.
Accurate detection of calcification and metal foreign bodies	Contrast agents have a considerably smaller risk of causing potentially lethal allergic reaction.
No risk to patient with implantable medical devices.	Evaluation of structures that may be obscured by artifacts from bone in CT

As previously mentioned, CT is considered as the standard medical imaging modality at the critical phase (see Fig. I. 8). This is because (1) CT modality has sufficient sensitivity to detect injuries requiring immediate surgery and (2) it is a fast technique, which allows for constant monitoring during the image acquisition. In addition, the display of hemorrhage and skull fractures at the hyperacute-acute phase is better with CT than with MRI (Bigler 1996).

However, CT does not have enough resolution to detect other type of lesions, such as diffuse lesions in TBI. MRI is very sensitive and accurate in diagnosing pathologies in brain injury patients. In particular, MRI is helpful in the sub-acute and chronic (or post-acute) settings, since MRI is superior to CT in detecting axonal injury, small areas of contusion and subtle neuronal damage (Ogawa et al. 1992). It is also better at imaging the brainstem, basal ganglia and thalamus (Lee, Newberg 2005). Regarding the question about which MRI acquisition sequence is better, a conclusive answer has not been found, since it strongly depends on the decision of the clinician and his/her clinical goal (as shown in Table I.5). However, most of the reviewed research papers use T1w or T2w MRI studies (Stamatakis, Tyler 2005); (Shen, Szameitat & Sterr 2008, Seghier et al. 2008a, Senyukova et al. 2011, Kruggel, Paul & Gertz 2008b, de Boer et al. 2009b, Bianchi et al. 2014a).

Table I. 5 Examples of the most common MRI acquisition sequences and the clinical uses associated to each other. (FLAIR: Fluid-Attenuated Inversion Recovery; DWI: Diffusion Weighted Imaging; ADC: Apparent Diffusion Coefficient; GRE: Gradient Echo; MRS: Magnetic Resonance Spectroscopy)

	T1W	T2W	FLAIR	DWI	ADC	GRE	MRS
Sub-acute Hemorrhage							
Chronic hemorrhage							
Anatomical details							
Edema							
Demyelination							
Embolic infarction							

Chronic infarctions							
Fat-containing structures							
Lesions involving brainstem and cerebellum							
Acute ischemia							
Infarcts							
Calcification							

In order to understand the role of these two imaging modalities in TBI and stroke, in the next paragraphs the common use of CT and MRI is explained.

Traumatic brain injury.

Not all TBI patients require neuroimaging (Nagy et al. 1999). CT is standardly the first imaging test performed in the emergency department setting for evaluation of head trauma. The goal of emergency imaging is to identify those lesions that need immediate treatment. MRI is commonly used to show lesions that could explain clinical symptoms and signs that are not explained by prior CT (Provenzale 2010). A recent study designed to compare CT and MRI for prediction of neurocognitive outcome has concluded that MRI is superior for lesion detection (Lee et al. 2008). TBI-related insults can appear as hyper-intensities or hypo-intensities, varying in magnitude and extent the degree to which they tend to correlate with clinical symptoms.

Stroke.

Imaging of the brain and vessels in patient with stroke in the acute stage has become a routine procedure used in daily clinical practice. Clinicians should follow two basic pathways when ordering imaging test in patients with acute stroke: (1) Imaging of brain and spinal cord and (2) imaging of the vessels (Culebras et al. 1997).

The imaging of the brain provide information that can guide patient treatment by: (a) identifying and determining the type of stroke; (b) localizing the lesion and (c) quantifying the lesion and determining the age of the lesion.

Imaging of the vessels is intended to clarify the mechanism of the stroke, whether thrombotic, embolic or hemodynamic and the risk of future events by: (a) identifying occlusive arterial disease; (b) localizing the occlusion in extracranial or intracranial vessels; (c) quantifying the degree of occlusion; (d) determining the pathology and (e) identifying other vascular lesions.

To sum up, CT and MRI modalities play an important role in brain injury diagnosis and management. These two neuroimaging studies contain a large amount of information about the lesions produced as a consequence of a TBI or stroke. CT is usually used at the hyperacute and acute stages to identify the origin of the brain injury and to establish a medical treatment as quickly as possible, since time lost is brain lost. MRI is more accurate to identify lesions and to make a prognosis. In next sub-section, the use of neuroimaging in neurorehabilitation is explained in detail.

I.1.4. Neuroimaging in neurorehabilitation

Most cases clinicians cursorily reviewed neuroimaging studies to get a sense of where the most obvious pathology may reside and some global indication of brain integrity, but generally not for prognostic decision-making (Bigler 2000).

Neuroimaging research on the predictive function of imaging findings in neurorehabilitation has been usually based on structural imaging modalities: CT and MRI, where the emphasis is to define the underlying visible pathology (Wilde, Hunter & Bigler 2012).

The first quantitative medical imaging measurement of pathology were linear measurements, such as the degree of midline displacement, width of a hematoma at its apex, etc. Nowadays, techniques for quantitative analysis permit a variety of methods that measure volume, surface area, thickness, shape and contour of any region of interest (ROI) (Wilde, Hunter & Bigler 2012). The most common quantitative analysis is a ROI volume measurement, which has relevance for predicting rehabilitation outcome, such as the relation between the hippocampal volume and memory outcome (Bigler, Wilde 2010).

Another quantitative neuroimaging technique referred to as voxel-based morphometry (VBM) (Ashburner, Friston 2000) classifies each pixel into white matter, gray matter and CSF and determines the relative concentration of different pixel types within a specified voxel. This technique can objectively demonstrate where differences among different subjects/patients occur. It is usually used to compare activation areas among different subjects.

According to (Wilde, Hunter & Bigler 2012), future neurorehabilitation studies will probably consider the totality of pathology identified, rather than focusing on a particular ROI or quantitative measure. (Strangman et al. 2010) have shown that memory rehabilitation improves if both global indicators of pathological changes in the brain are combined with specific quantitative changes in target ROIs like the hippocampus known to be a critical region participating in the function being rehabilitated. Newer methods of image analysis should change the way rehabilitation clinicians' view and use neuroimaging findings and the kind of information that can be gathered from a neuroimaging assessment. Template databases are being developed so the volume, size and shape of a critical structure can be determined (Wilde, Hunter & Bigler 2012).

Nowadays, there are at least two challenges related with neuroimaging on brain injury and on neurorehabilitation: (1) the design and development of analysis and processing techniques to extract structural impairment information to be used as an objective parameter to prescribe and to assess neurorehabilitation treatments and (2) new data management strategies to classify and store this source of high-quality information through metadata, since big data in neuroimaging is a reality.

In the next sub-section, these ideas are described in detail as they constitute the problem statement and justification of this PhD Thesis.

I.2. Problem statement and justification of the research

The present PhD work falls under the research line on ‘Neurorehabilitation Engineering’, of the Bioengineering and Telemedicine Centre (GBT) at Escuela Técnica Superior de Ingenieros de Telecomunicación (ETSIT), Universidad Politécnica de Madrid (GBT-UPM 2015). This research work is performed in close collaboration with Institut Guttmann (Institut Guttmann - Neurorehabilitation Hospital 2014). In particular, this PhD Thesis is focused on the sub-line ‘Analysis and classification of structural alterations resulting from an acquired brain injury based on medical imaging’. The main purpose of this sub-line is to develop new biomedical technologies to (1) define and develop algorithms for automatically identifying brain lesions associated to brain injury; (2) contribute to the creation of a cognitive dysfunctional profile and (3) define and create a knowledge database containing imaging studies and clinical reports.

GBT was founded in 1983, the mission of the centre has been the training, research and technological development in the field of bioengineering and biomedical engineering. The main research areas are: ambient assisted living; bio-electromagnetism; bioinstrumentation and nanomedicine; biomedical imaging; knowledge management and data mining; diabetes technology; neurorehabilitation engineering; telemedicine and intelligent devices; and surgical simulation, planning and image guided surgery (Fig. I. 12).

Figure I. 12 Bioengineering and Telemedicine Centre (GBT) at Escuela Técnica Superior de Ingenieros de Telecomunicación (ETSIT), Universidad Politécnica de Madrid

Institut Guttmann, founded in 1965, it was the first hospital in Spain especially caring for people with acquired spinal cord injury and brain damage. Nowadays, it is a leading hospital in the medical treatment, surgery and full rehabilitation of patients with spinal cord injury, acquired brain damage or any other neurological disability. Its goal is to provide the most comprehensive, customized and specialized medical and rehabilitation care at the highest human, scientific and technical level. Its modern facilities, a team of nearly 400 practitioners and a record of 17,000 patients treated make Institut Guttmann into one of the most advanced, world-class hospitals of its kind (Fig. I. 13).

Figure I. 13 Institut Guttmann

The research under this PhD is part of the **COGNITIO** project: Multiparametric analysis of image, clinical data and therapy for the optimization of cognitive rehabilitation on TBI (TIN2012-38450-C03). This project is funded by the Spanish Ministry of Economy and Competitiveness. The project's consortium is composed by an interdisciplinary clinical and technological team, with a long investigative experience in the application field, and proficient in research areas related to biomedical engineering, telemedicine, image processing, artificial intelligence, data mining and cognitive neurorehabilitation. Involved partners are research groups from the Universidad Politécnica de Madrid, the Instituto de Investigación de Inteligencia Artificial del CSIC and the Institut Guttmann.

This research project aims to increase knowledge in the field of rehabilitation theory based on cognitive disability. Cognitive rehabilitation aims to reduce the impact of the disabling conditions in order to reduce functional limitations and increase patient's autonomy. In order for the rehabilitation process to be more effective, treatments must be intensive, personalized to the patient's condition and evidence-based; and require constant monitoring. Currently, there is a lack of knowledge regarding patients' disability profiles (cognitive or structural) and the combination of therapeutic tasks that optimize the treatment's effectiveness.

This research will serve as a previous step to the creation of personalized therapeutic interventions based on clinical evidence. In particular, the main goal of this research project is to foster knowledge in the following scientific and technological areas:

1. Physio-pathological mechanisms involved in ABI cognitive rehabilitation.
2. Neuroimaging processing techniques for the classification and categorization of ABI-based structural lesions.
3. Automatic learning techniques for real-time and personalized therapies
4. Knowledge inference, data mining and multi-parametric analysis applied to clinical data for therapeutic treatment optimization.

Fig. I. 14 shows the interrelationships and interactions among these four technological areas.

Figure I. 14 Interrelationships and interactions among the four main technological areas of COGNITIO project.

In other words, medical rehabilitation has usually been compared with a black box because the processes by which clinic treatments, medications, education, technical aids and other interventions transform inputs (impairments and activity limitations) into outcomes (improved functioning, quality of life and independence) remain largely unknown (Dijkers et al. 2014). No indication was given to explain why patients in rehabilitation improve and which of the various treatments, for what patient groups, in what strength or in what time frame are effective (Bode et al. 2007). The main reasons to explain this lack of theory is that (1) treatments must be described by their clinical activities and patient's data. Researches should offer a theory as to how these information sources, through a mechanism of action, try to improve functional and cognitive impairments of brain injury patients (Whyte et al. 2014); and (2) almost all rehabilitation research is underdeveloped, not only in its theory underpinnings but also in specifying the information that might be used by other in replicating the investigation (van Heugten, Wolters Gregório & Wade 2012).

Nowadays, the treatments are planned considering the results obtained from a neuropsychological assessment battery, which evaluates the functional impairment of each cognitive function (memory, attention, executive functions, etc.). One of the most important proposals of COGNITIO is to define a cognitive dysfunctional profile based on four knowledge sources: (1) *neuroanatomical structures*: brain structures described in literature; (2) *cognitive functions*: a set of cognitive functions defined in the neuropsychological body of knowledge; (3) *neuropsychological assessment data*: data from the neuropsychological initial evaluation of ABI patients; and (4) *neuroimaging studies*: neuroanatomical information (Luna et al. 2014), shown in Fig. I. 15. This profile may be integrated into the body of knowledge of the neurorehabilitation discipline, in such a way that this body of knowledge will consist of (1) the relations among structural damage, (2) cognitive impairment profile and (3) clinical intervention results.

Figure I. 15 Cognitive dysfunctional profile – COGNITIO project.

This PhD Thesis focuses on the design and development of new neuroimaging processing techniques mentioned in point 2 of the described scientific and technological areas of COGNITIO or according to Fig. I. 15, in point 4. Mere clinical reading of a scan may offer the clinician general impressions of the health or impairment of the brain, but by using new automated methods to analyze and process medical imaging studies, more precise and direct assessment of the brain can be offered, and this will likely result in better directed therapies (Wilde, Hunter & Bigler 2012). Thus, there is a clear need for the development of new analysis and processing methods to automatically identify brain lesions.

The goal of this thesis is to contribute towards improving the extraction of information from neuroimaging studies of brain injury patients to automatically identify lesions. Improvements in imaging analysis technology might allow not only standard clinical scans (MRI) to be converted into accurate lesion maps, paving the way for automated prediction and storing software; but also to set possible correlations among structural impairment, the cognitive dysfunctional profile and the most appropriate rehabilitation tasks.

Within this context, this research work proposes new algorithms to automatically identify lesions that may be used both for contributing to the cognitive dysfunctional profile and for extracting metadata in order to create a structured database. Fig. I.16 shows the main research areas of this thesis.

Figure I. 16 Main research areas

Manual delineation of brain anatomical regions is the classical approach to identify areas of interest. Manual approaches present several problems related to inconsistencies across different clinicians, time and repeatability. Automated delineation is done by registering brains to one another or to a template (Klein et al. 2009). However, when imaging studies contain lesions, there are several intensity abnormalities and location alterations that reduce the performance of most of the registration algorithms based on intensity parameters. Thus, specialists may have to manually interact with imaging studies to select landmarks or identify regions of interest. These two solutions have the same inconvenient that manual approaches, mentioned before.

In order to automate the identification of lesions, this PhD proposes to use not only intensity but also spatial information. The use of these two types of information permits to characterize the anatomical brain structure underlying to the injured area. Descriptors are algorithms which combine these two types of information. Fig.I.17 shows the proposed methodology and its direct applications. The methodology consists of four main stages: (1) pre-processing, (2) singular points identification, (3) registration and (4) lesion detection. In the pre-processing stage, medical imaging studies are normalized to a common intensity and spatial reference system. Singular points identification stage automatically detect landmarks. This stage is equivalent to the manual marking of landmarks by the clinician. In the registration stage, the two medical imaging studies are put into correspondence based on the identified singular points. Finally, in the last stage anatomical structures that may be injured are identified and the information is displayed through a report or with a color code over the original imaging study.

Figure I. 17 Proposed methodology and direct applications of the developed algorithms.

Regarding the most important direct applications, the contribution to the dysfunctional profile generation should be highlighted. This profile may allow to design evidence-based and personalized neurorehabilitation treatments. This is one of the main proposals of COGNITIO project and combines theoretical, imaging and clinical information. This PhD is focused on the imaging information contribution, whereas the extraction and organization of theoretical and

clinical information is treated in other PhD developed in this group by Ruth Caballero, as shown in Fig. I. 18

Figure I. 18 Dysfunctional profile generation.

Other important direct applications are the use of lesion information as metadata to create neuroimaging databases and the integration of these algorithms in existing neuroimaging tools.

I.3. Thesis outline

This thesis is structured in seven sections:

- *Section I*: Introduction.
- *Section II*: Research hypotheses and objectives.
- *Section III*: State of the art.
- *Section IV*: Material and methods.
- *Section V*: Results
- *Section VI*: Conclusions and future works.

Section I has established the foundations of this PhD, focusing on the clinical and technical context related to brain injury. This section establishes the problem statement and the justification of the research.

Section II will present the hypotheses that drive this research, as well as the specific objectives to meet in this PhD work.

Section III will present the state of the art for the lesion identification algorithms used on neuroimaging applications. The conclusions of this state of the art leads to analyze the state of the art of each stage of the proposed methodology. It will include also the state of the art of two direct applications of the proposed algorithms developed in this research work.

Section IV will present the materials used through this research work. It will also describe the algorithms proposed in each of the stages of the proposed methodology.

Section V will present and discuss the results obtained in each stage.

Section VI will present the conclusions extracted from this research. Each hypothesis postulated in Section II will be discussed, and the main contributions of this PhD will be presented. Finally, guidelines and directions for future works based on the results obtained will be given.

II Research hypotheses and objectives

In which the research hypothesis and objectives of the state of this PhD are described.

<" As long as our brain is a mystery, the universe, the reflection of the structure of the brain will also be a mystery" – Santiago Ramón y Cajal>

II.1. Research Hypotheses

The research hypotheses that have shaped this Doctoral Thesis are described below.

II.1.1. General hypothesis

H1 – The development of automatic methods for processing and analyzing medical imaging studies and the combination of them with techniques to classify extracted data, make it possible to automatically define the structural impairment profile of the patients.

II.1.2. On the feature extraction of medical imaging studies

H2 – The automatic classification and characterization of brain MRI studies permits to extract important information of images that it is not used nowadays. In addition, it facilitates the improvement of the body knowledge associated with the neurorehabilitation by integrating multi-parametric information.

H3 – The combination of intensity variation information and spatial location information through descriptors permits to uniquely characterize a brain MRI study. This resulting information can also be considered as metadata in medical imaging database techniques.

H4 – The use of descriptors in the field of medical imaging permits the design and development of a registration algorithm based on singular points. This registration algorithm works properly under intensity variation conditions within brain MRI studies.

II.1.3. On the automatic lesion detection in brain injury patients

H5 – Non rigid registration algorithm based on descriptors permits to detect and locate anatomical brain structures whose size or position have changed compared to the anatomical brain structures identified in an atlas of control subjects.

H6 – The statistical study of brain atlas permits to characterize anatomical structures on control subjects. Therefore, this statistical study allows to identify which anatomical structures have changed their area/volume and/or the position of their centroid with a reliability measure.

II.1.4. On the quality evaluation of lesion identification

H7 – The development of metrics to objectively assess the quality of the lesion identification provides significant information about the reliability of such identification.

II.2. Objectives

II.2.1. General objective

The main objective of this PhD thesis is the design, implementation and validation of new methods for processing and analyzing brain MRI studies in order to automatically detect structural lesions in brain injury patients.

II.2.2. Specific objectives

O1 – The design, development and validation of a methodology to automatically process and analyze brain MRI studies for identifying possible brain lesions in brain injury patients and the reliability of the detection.

O2 – The design, development and validation of algorithms to identify singular points in brain MRI studies based on descriptors. More specifically, the objective contemplates: (1) the use of a multi-detector framework to identify different types of singular points, (2) the characterization of the neighborhood of each type of singular point based on descriptors and (3) the development of two new descriptors adapted to MRI studies in a 2D version and in a 3D version.

O3 – The design, development and validation of a non-rigid registration algorithm based on descriptors to improve the results in brain MRI studies with intensity variations under the presence of brain lesions.

O4 – The design, development and validation of an algorithm to identify brain lesions based on the statistical study of anatomical brain atlas of control subjects. This algorithm not only identifies those structures that have changed their centroid position and area/volume, but it also computes the reliability of the detection.

O5 – The design and development of assessment metrics and the integration of these metrics in an evaluation methodology to quantify the quality of the implemented algorithms

III State of the art

In which the state of the art related to the research hypothesis is presented. This chapter aims to present an overview of the environment and to show published research papers dealing with similar goals.

<"Every man can, if he so desires, become the sculptor of his own brain" – Santiago Ramón y Cajal

III.1. Introduction

As mentioned in the previous chapters, the main objective of this PhD work is to design and to implement new methods for automatically identifying brain injury lesions. This information may be used both for improving the personalization of neurorehabilitation treatments through the cognitive dysfunctional profile and as metadata to design databases, as shown in Fig. III. 1.

Figure III. 1 Research goals and applications

In order to understand the problem addressed within the conceptual framework of this PhD, this chapter reviews the state of the art in automated lesion identification algorithms applied to brain injury patients. The outcome of this review will identify the strengths and weaknesses of the current algorithms. Based on these weaknesses, we will propose and design a new methodology and new algorithms to this extent.

As a consequence of the new proposals, it is necessary to describe the state the art in this type of algorithms. Therefore, this chapter also includes the state of the art of the new proposed algorithms. Since the new proposed methodology is made up of four main stages, this section will be divided into four parts. In the first one, pre-processing algorithms are reviewed. Then, algorithms to identify features on imaging studies, and in particular in brain, are described. This part also explains what a descriptor is and where they are commonly used. In the third part, registration algorithms in brain injury applications are reviewed. The state of the art of registration algorithms can be as large as wanted, but in order to focus on the application context of this PhD work, only those algorithms whose major application is the scope of neuroimaging have been analyzed. Finally, the fourth part is about the detection of lesions. This part is an original contribution of this PhD. since, we do not detect any specific algorithm to be analyzed.

It is also important to know the state of the art in neuroimaging tools and neuroimaging databases (please refer to Section III.3 and III.4, respectively), as they are two of the most relevant direct applications of the extracted information by the proposed methodology. Fig.III.2 shows the structure of this chapter.

Figure III. 2 Structure of the State of the Art chapter.

III.2. Lesion Identification Algorithms

III.2.1. State of the Art

The automated identification of lesions in medical imaging studies is one of the main challenges of many medical areas, since the information extracted from these studies is not only quantitatively but also qualitatively better. This information may be used mainly to make accurate medical diagnosis and prognosis, to improve clinical treatments and to personalize rehabilitation treatments. These algorithms are commonly used in 'Computer-Assisted Diagnosis' systems. The number of scientific publications about automated lesion identification has considerably increased in the last years, as shown in Fig.III.3.

Figure III.3 Published items in each year: 'lesion detection', 'medical imaging', 'automated'. Source: Web of Science (<http://apps.webofknowledge.com/>)

The identification of lesions is mainly performed by applying: (1) registration and segmentation algorithms or (2) registration and feature extraction. Registration is usually a common stage in most of the reviewed algorithms. Fig.III.4 shows the medical areas of the reviewed research papers. Neurology and ophthalmology have the greatest number of research papers about the automated lesion detection. Most of the neurology papers are related to the

detection of lesions on multiple sclerosis (MS), epilepsy, brain tumors and Alzheimer. However, the algorithms that have been developed for lesion detection on TBI and stroke are less numerous (around a 10% of the neurology papers).

Figure III. 4 Distribution of research contributions in medical areas. (Web of Science: WOS)

As mentioned before, although many scientific papers are related to neurology, most of them are used to identify lesions associated with brain tumors and neurodegenerative diseases such as multiple sclerosis and Alzheimer. In order to examine the state of the art of lesion detection algorithms in stroke and TBI in depth, a systematic review of the state of the art in this concrete subject is summarized in Table III.2. This review has been performed using the Web of Science (WOS) and the key words: ‘lesion detection’, ‘medical imaging’, ‘automated’, ‘stroke’ and ‘traumatic brain injury’.

Table III. 1 Overview of the current lesion detection methods for MRI Data (TBI and stroke)

Reference	Brief Description	Disease	IM	Pros (+) and Cons (-)
(Braun et al. 2000)	It is based on a histogram-based segmentation technique, combining multimodality images.	Stroke	MRI	+ Multimodality images. - Only based on intensity information. - Only gives quantitative information.
(Fiez, Damasio & Grabowski 2000)	The objectives of this study were to determine the sources and magnitude of variability involved in lesion segmentation and warping using a manual and an automated technique.	Both	MRI	+ Uses voxel information. - Only identifies tissue lesions. - Only based on intensity information.
(Anbeek et al. 2004)	Direct KNN classification with spatial information using previously known lesions in the training set	WM Lesion	MRI	+ Uses spatial information. - It only detects predetermine lesions

				<ul style="list-style-type: none"> - The registration algorithm is not scale to large data.
(Stamatakis, Tyler 2005)	It preprocesses the imaging study and compares this study with a control subject image database to identify injured Broca's area.	Both	MRI	<ul style="list-style-type: none"> + Compares with control subjects. - Only intensity based information is used.
(Kruggel, Paul & Gertz 2008a)	In order to create a probability map of injury, it proposes to use co-occurrence features with PCA and the distance to cluster centers.	WM Lesion	MRI	<ul style="list-style-type: none"> + High dimensional texture features - Registration assumes single cluster per class - Only intensity based information is used.
(Seghier et al. 2008b)	Tissue segmentation followed by outlier detection in the GM and WM.	Both	MRI	<ul style="list-style-type: none"> + Tissue classification with an iteratively learned abnormal class. - Smoothing cause problems with small lesions.
(Shen, Szameitat & Sterr 2008)	This paper proposes a segmentation algorithm based on c-mean fuzzy logic and tissue probability maps.	Stroke	MRI	<ul style="list-style-type: none"> + Uses tissue probability maps. - Only applicable to stroke - Only intensity based information is used.
(de Boer et al. 2009a)	K-nearest neighbor for initial tissue segmentation. Gray matter is reclassified to lesion or non-lesion using FLAIR.	WM Lesion	MRI	<ul style="list-style-type: none"> + Uses known tissue location priors for misclassification - Registration is specific for the described disease. - Detects lesion on tissue not on anatomical structures.
(Sun, Bhanu & Bhanu 2009)	Asymmetry detection followed by classification.	Stroke	MRI	<ul style="list-style-type: none"> + Not based on known information. - Only intensity based information is used. - Problems with symmetrical lesions.
(Senyukova et al. 2011)	This research work proposes a method to identify isointensity curves to detect lesions on certain diffuse axonal damage	TBI	MRI	<ul style="list-style-type: none"> + Delineates contours. - Intensity based only - Region of interest information
(Ong et al. 2012)	WM lesions are detected as outliers in the intensity distribution of the FLAIR MRI using an adaptive outlier detection approach. Outliers are detected using a novel adaptive trimmed mean algorithm and box-whisker plot.	WM lesions - stroke	MRI	<ul style="list-style-type: none"> + Uses at least two types of MRI modalities. - Only uses one type of information: intensity. - Only quantification information.
(Shi et al. 2013)	It proposes a segmentation algorithm based on a coarse-to-fine mathematical morphology method.	WM Lesion - stroke	MRI	<ul style="list-style-type: none"> + Multimodality images + Shows information about injured anatomical structures. - Only based on intensity information.
(Riad et al. 2013)	The goal is to identify individual lesions on multimodality images. It is based on a classificatory.	WM Lesion - Stroke	MRI	<ul style="list-style-type: none"> + Multimodality images. - Only intensity based information is used.

(Bo Wang et al. 2013)	This paper proposes a methodology to obtain biomarkers on TBI imaging studies. These markers are: cortical thickness, volume changes and global geometric deformations.	TBI	MRI	+ Multiple parameters to describe brain injury. - Only quantitative analysis.
(Bianchi et al. 2014b)	It proposes a contextual model to estimate the progression of the disease using subject information, such as the time since injury and the location of the TBI.	TBI	MRI	+ Combines patient information, texture features. - Unimodal MRI - mTBI specific model
(Bianchi, Bhanu & Obenaus 2015)	Static and dynamic context features are integrated into a discriminative voxel-level classifier	TBI	MRI	+Integrates spatial with visual information - Only mTBI lesions - Only has been tested on rats.

All the previous research works use MRI, in particular most of them use T1w and/or T2w MRI studies. Generally, the goal of most of these papers is to detect injured white matter or lesions in concrete functional areas such as the Broca's area. In other words, these papers try to identify injured regions of interest, but they do not detect the totality of pathology along the imaging study. Nevertheless, it is important to point out that no research works have been found whose final objective is the automated detection of the totality injured anatomical structures on medical imaging associated with brain injury.

It is important to highlight that no research paper shows any technique to display the detected lesions. All but one (Shi et al. 2013) only take into account quantitative information. According to (Strangman et al. 2010), the combination of quantitative measures with global indicators improves the rehabilitation of a particular brain function.

All but two research papers (Anbeek et al. 2004, Bianchi, Bhanu & Obenaus 2015) are used only on intensity imaging information to detect lesions. According to (Joel Ramirez, Fu Quiang Gao, Sandra E. Black 2008), pathological changes on anatomical structures are always associated with intensity abnormalities and/or location alterations. Therefore, the combination of both intensity and location information can help develop a deeper knowledge on the complex brain structure-function relations on brain injury (Wei et al. 2002, Ramirez, Gao & Black 2008).

In conclusion, there is a need for designing and developing new algorithms to globally identify injured anatomical structures based not only on intensity but also on spatial information.

III.2.2. Proposed Methodology

Labelling regions is important to characterize the morphometry of the brain, and therefore to identify anatomical structures that may be injured. In particular, brain morphology measures have been used to identify many anatomical structures (Klein, Tourville 2012).

Manual delineation of brain regions is the classical approach for establishing anatomical correspondence. However, manual labeling techniques suffer from inconsistencies within and across human labelers (Klein et al. 2009, Fiez, Damasio & Grabowski 2000, Towle et al. 2003); are very time-consuming processes (Bianchi et al. 2014b), hindering their extensive clinical use (Powell et al. 2008); and requires a trained operator to improve inter and intra rater reliability,

large data sets for statistically sound analysis and multi-modal inputs as there are several types of alterations associated with TBI or stroke on MRI (Bianchi et al. 2014b).

Automatically determining anatomical correspondence is almost universally done by registering brains to one another or to a template (Klein et al. 2009). Lesions introduce topological differences varying in magnitude and are always associated with intensity abnormalities and/or location alterations (Rodriguez-Vila, Garcia-Vicente & Gomez 2012). These alterations cause that physical one-to-one correspondence between images may not exist due to the insertion or removal of some imaging content. This inconsistency between two image studies could severely reduce the performance of registration algorithms based on intensity imaging parameters. As a consequence, specialists may have to manually interact with the affected region on the scans or select manual landmarks to compute the spatial transformation between studies. Nevertheless, both possibilities have the same drawbacks of the manual delineation highlighted above.

The automation of the landmarks' selection process can be done using the combination of intensity and location information, and may help develop algorithms to automatically identify changes associated with lesions (Wang et al. 2010). Descriptors are algorithms, as explained below, that combine intensity and location information to detect singular points on images. Registration algorithms based on descriptors have begun to be used on several medical imaging applications. Fig.III.5 shows the methodology to automatically identify brain lesions, it consists of four main stages: (1) pre-processing, where the brain studies are normalized to a common intensity and spatial reference system; (2) singular points identification, where imaging features are automatically identified (This stage is equivalent to the manual marking of landmarks by the researcher/clinician); (3) registration, where the transformation to put into correspondence two medical imaging studies is computed; and (4) lesion detection, where the anatomical structures that may be injured are identified. The state of the art of each stage is analyzed in next sub-sections.

Figure III. 5 Proposed methodology to automatically identify brain lesions.

III.2.2.1 Pre-processing

III.2.2.1.1 Introduction

The pre-processing stage usually involves a spatial and intensity normalization. In most methodologies used to analyze neuroimaging studies, in first place, a skull-stripping is performed. The goal is to remove the skull from images, leaving only the region occupied by actual brain tissue. Then, an intensity normalization is usually computed. This type of

normalization brings MR intensities to a common scale by adjusting the variation range of the histogram. Finally, spatial normalization is applied. This normalization transforms the data to the same stereotactic space by registering the source to the template study by applying a rigid algorithm.

Figure III. 6 Workflow of a common pre-processing stage.

III.2.2.1.2 Skull – stripping

Most of the morphometric studies of brain MRI often require a preliminary step of isolate brain from extracranial or ‘non-brain’ tissues (Fennema-Notestine et al. 2006a). This step, commonly referred to as ‘skull-stripping’, facilitates image processing such as surface rendering (Dale, Fischl & Sereno 1999), cortical flattening (van der Kouwe et al. 2008), image registration (Shen, Davatzikos 2004) and tissue segmentation (Shattuck et al. 2001).

To extract the brain researchers numerous algorithms based on: (1) morphology operations or region growing; (2) atlas matching; (3) histogram analysis; (4) watershed; (5) graph cuts; (6) level sets; (7) deformable models; (8) label fusion; and (9) hybrid approaches (Huang et al. 2014) have been developed.

Algorithms based on **morphology operations** generates a mask by applying thresholding, connectivity, surface detection and morphologic operators. Examples of this type of skull-stripping algorithms are: (Ward 1999, Lemieux et al. 1999, Chiverton et al. 2007, Mikheev et al. 2008, Park, Lee 2009). **Atlas matching** algorithms (Ashburner, Friston 2000, Dale, Fischl & Sereno 1999) involve a voxel-wise comparison of intensity levels between an atlas and a subject/patient study. **Histogram analysis** algorithm is divided into three steps: background thresholding, disconnection of brain from skull and removal of residue fragments (Shan, Yue & Liu 2002). **Watershed** –based algorithm interprets each slice of an MRI study as a topographic map composed of several hills corresponding to bright image areas and valleys corresponding to dark image areas (Hahn, Peitgen 2000). **Graph cuts** –based algorithms use a graph theoretic image segmentation technique to position cuts that isolate and remove non-brain tissues (Sadanathan et al. 2010). **Level sets** algorithms are based on the propagation of an initial region towards the desired boundaries through iterative evolutions (Baillard, Hellier & Barillot 2001, Zhuang, Valentino & Toga 2006, Khan et al. 2011). **Deformable models** – based algorithm use a deformable model evolving to fit the brain’s surface by the application of a set of locally adaptive model forces (Smith 2002a). **Label fusion** –based algorithms compare the target study to all the atlases in a template library. Best-matches atlases are then selected and the labels in the selected ones are propagated to the target image (Leung et al. 2011, Eskildsen et al. 2012, Buades, Coll & Morel 2005). **Hybrid approaches** combine some of the aforementioned techniques (Shattuck et al. 2001, Huang et al. 2014, Ségonne et al. 2004, Rex et al. 2004, Rehm et al. 2004, Iglesias et al. 2011, Carass et al. 2011, Shi et al. 2012).

Each of these methods presents pros and cons. According to (Huang et al. 2014), morphology operations are fast and can be easily adjusted, but these methods usually fail to

determine the optimum morphology size necessary to separate brain tissues from non-brain tissues. Histogram and watershed algorithms are simple and obtain accurate results delimitating boundaries. In contrast, these methods are sensitive to noise. Deformable models – based algorithms assume that the brain surface is smooth with low curvature. However in some regions such as the basal ones, this characteristic is not often observed in brain boundary. Label fusion algorithms have been widely analyzed (Hartley et al. 2006, Fennema-Notestine et al. 2006b). Although these algorithms provide optimum performance for skull-stripping, a number of fundamental problems of label fusion, such as the estimation of the labels of test samples by linearly combining the labels of training samples and the fusion weights mechanism are unclear and require further research.

III.2.2.1.3 Intensity Normalization

Intensity variation among different MRI studies is fundamentally due to the fact that there are different protocols of MRI scan acquisitions, different manufacturers, scanner-models but also due to the fact that scans from various sites can correspond to patients at varying stages of the disease, as the presence of pathology can impact the tissue intensity behaviors significantly (Shah et al. 2011). A lack of standard intensity makes it difficult to generalize the behavior of the different type of tissue in the presence of disease. Therefore, it is necessary to bring MR intensities to a common scale by adjusting the variation range of the histogram.

Various normalization algorithms have been proposed to deal with intensity scale inhomogeneity. These algorithms are classified into: (1) even-order histogram derivatives, (2) template histogram matching, (3) region-specific normalization; (4) non-linear registration; (5) density functions and (6) hybrid approaches (Shah et al. 2011).

Even-order histogram derivatives algorithm depends on the even order derivatives of the image histogram. These derivatives were chosen by optimizing an error function computed from simulated image histograms (Christensen 2003). **Template histogram matching** algorithm aims at changing global statistics of the MRI template histogram while preserving local feature contrast. By minimizing the Kullback-Leibler divergence measure between the two densities (Weisenfeld, Warfteld 2004b, Roy, Carass & Prince 2013). **Region-specific normalization** algorithm approximates the source and the target histograms by using a Gaussian Mixture Model (GMM). Then, a polynomial correction is applied to smooth the intensity values (Hellier 2003). **Non-linear registration** algorithm considers the probability densities of tissue types as images and apply a distance measure based non-rigid registration to the joint histograms resulting in a non-linear correction function for MRI intensities (Jäger et al. 2006). **Density functions** – based algorithm requires the specification of the class conditional probability density functions. The densities are derived interactively from pre-identified representative training voxels. Then, the method uses an interactive expectation maximization algorithm to refine the parameter estimation for both classification and intensity normalization (Wells III et al. 1996). **Hybrid** algorithms are based on the combination of the quartiles and deciles, in particular the median corresponding to the foreground in the image, to established the ‘standard’ intensity range (Nyúl, Udupa & Zhang 2000, Nyu, Udupa 1999).

III.2.2.1.4 Spatial Normalization

Spatial normalization is the process of standardizing images of different subjects into the same anatomical space, since human brain differs significantly in size and shape (Rosario et al. 2008). Therefore, the objective of spatial normalization is to remove, to some extent, anatomical variability between the subjects' imaging studies to allow analysis of the data.

Several techniques are available to perform spatial normalization nowadays. Most current spatial normalization methods use automated image-matching algorithms (Ashburner, Friston 1997, Brett, Johnsrude & Owen 2002, Toga et al. 2006). One of the most widely used normalization software in the research literature is Statistical Parametric Mapping (SPM) (Wellcome Trust Centre for Neuroimaging 2015). This approach works by minimizing the average across voxels of the squared difference between the volume to be normalized and a template volume. However, these methods cannot be used in brains containing lesions. (Crivello et al. 2002, Gispert et al. 2003, Robbins et al. 2004, Hosaka et al. 2005, Wu et al. 2006, Crinion et al. 2007) compare and assess different spatial normalization approaches. In all of them, brain atlases are used as template and a registration algorithm is commonly used to put into correspondence the atlas with the subject/patient MRI study. The following paragraphs will review the state of the art in brain atlases. Regarding the state of the art in registration algorithms, please refer to section III.2.2.3.

Brain atlases define spatial characteristics of the brain. In the last two decades, there have been an increasingly research interest in developing brain atlases. They allow for a quantitative characterization of the (1) normal variability of certain metrics across a population, (2) the relationship between those metrics across a population and (3) the detection of subtle changes associated with disease, genotype, gender or demographics (Evans et al. 2012). It has to be taken into account that the construction of a realistic anatomical brain atlas is a time-consuming task. Because of this, public atlas repositories have been created to provide the research neuroscientist with MRI data. According to (Cabezas et al. 2011), atlases can be classified into (1) topological and (2) probabilistic atlas, depending on whether the atlases are based on a single subject or on populations. Another classification is based on research purposes. According to this classification, there are two main type of atlases: (1) whole brain adult atlases and (2) domain specific atlases (shown in Fig.III.7) (Evans et al. 2012).

Figure III. 7 Classification of brain atlases according to research or clinical purposes. (Evans et al. 2012)

Whole brain atlases consist on single subject or populations based atlases. The goal of these atlases are to establish an anatomical topography map of the brain. These atlases can be subsequently divided into *Tallairach space*, *MNI space* and *volumetric parcellation*. The first two

type of atlases do not usually contain manual segmentations of MRI images, whereas the volumetric atlases contain manual segmentations or annotations performed by expert radiologist (See Table III.4 for further information).

Domain specific atlases are atlases of specific populations, tissues or brain areas. *Pediatric brain* atlases carefully characterize normative pediatric population (Evans, Brain Development Cooperative Group 2006, Fonov et al. 2011). *Aging brain* atlases provide normative data from elderly control subjects. OASIS ('Open access series of imaging studies') (Marcus et al. 2010) and ADNI ('Alzheimer disease neuroimaging') (Weiner et al. 2010) are examples of this type of atlases. *White matter* atlases characterize white-matter fiber tract commonly used to examine fMRI-based studies of functional connectivity (Wassermann et al. 2010, Thiebaut de Schotten et al. 2011). *Surface* atlases extract the cortical surfaces from each subject and build an averaged surface template (Thompson, Toga 1996, Van Essen 2005, Lyttelton et al. 2007, Auzias et al. 2011). *Regional* atlases focus on certain localized brain areas such as the cerebellum (Schmahmann et al. 2000). *Disease-specific* atlases are often used as priors for subsequent lesion classification such as multiple sclerosis (MS) (Van Leemput et al. 2001, Zijdenbos, Forghani & Evans 2002) or Alzheimer (Oishi et al. 2009).

III.2.2.1.5 Analysis and Conclusions

In this section algorithms related to the pre-processing have been reviewed and analyzed with the aim to propose a series of ideas that will be used throughout this PhD:

- The huge variability of shape and size brains makes necessary to pre-process neuroimaging studies before processing and analyzing them.
- The pre-processing stage is divided into three main steps: skull-stripping, intensity normalization and spatial normalization. Despite the large number of different methods developed with these goals, neither certain algorithms nor a protocol has been established within the neuroscience community.
- To establish a common intensity and spatial reference, it is critical and it affects directly in the quality of the obtained data.

Table III.2, III.3 and III.4 summarize the state of the art in skull-stripping algorithms, intensity normalization algorithms and brain atlases. Registration algorithms are reviewed in section III.2.2.3.

Table III. 2 Summary table of skull-stripping algorithms.

Algorithm Classification	Pros (+) and Cons (-)	Reference
Morphology operations or region growing	+ Fast and easily adjusted. - Fail to determine the morphology size.	(Ward 1999, Lemieux et al. 1999, Chiverton et al. 2007, Mikheev et al. 2008, Park, Lee 2009)
Atlas matching	+ Fast - Results depend on intensity information.	(Ashburner, Friston 2000, Dale, Fischl & Sereno 1999)
Histogram analysis	+ Simple and accurate results delimitating boundaries. - Sensitive to noise	(Shan, Yue & Liu 2002)

Watershed	+ Simple and accurate results delimitating boundaries. - Sensitive to noise	(Hahn, Peitgen 2000)
Graph cuts	- Predetermine results	(Sadanathan et al. 2010)
Level sets	- Highly dependent on the initialization.	(Baillard, Hellier & Barillot 2001, Zhuang, Valentino & Toga 2006, Khan et al. 2011)
Deformable models	- Problems with sudden curvatures.	(Smith 2002a)
Label fusion	+ Good results - Not clear method to estimate labels.	(Leung et al. 2011, Eskildsen et al. 2012, Buades, Coll & Morel 2005)
Hybrid approaches	+ Good results + Accurate - Results depends only on intensity information.	(Shattuck et al. 2001, Huang et al. 2014, Ségonne et al. 2004, Rex et al. 2004, Rehm et al. 2004, Iglesias et al. 2011, Carass et al. 2011, Shi et al. 2012)

Table III. 3 Summary table of intensity normalization algorithms.

Algorithm Classification	Pros (+) and Cons (-)	Reference
Even-order histogram derivatives	+ It optimizes an error function - It needs a threshold-sensitive brain segmentation algorithm to work properly.	(Christensen 2003)
Template histogram matching	+ Good results - Slow computational speed.	(Weisenfeld, Warfield 2004b, Roy, Carass & Prince 2013)
Region-specific normalization	- It should not be applied on a skull-stripped image. - The results depend on the region of interest.	(Hellier 2003)
Non-linear registration	+ Good results - Slow	(Jäger et al. 2006)
Density functions	+ It shows good results. - Time consuming process - Semi-automatic	(Wells III et al. 1996)
Hybrid approaches	+ It does not sacrifice accuracy for gains in speed. + Adaptable to different brain regions. + It does not rely on specific statistical properties. - Limitations in the presence of pathologies.	(Nyúl, Udupa & Zhang 2000, Nyu, Udupa 1999)

Table III. 4 Summary table of Whole brain adult atlases

Name	Reference	MRI modalities	Average Age	No. subjects	No. structures
Talairach					
Talairach	(Talairach 1967)	---	60	1	52 Brodmann areas
MNI					
MNI305 T1	(Evans, Collins & Milner 1992, Evans et al. 1992, Evans et al. 1993)	T1	23.4±4.1	305	---
Colin27 T1	(Holmes et al. 1998)	T1	---	1	---

MNI152 – ICBM152	(Mazziotta et al. 1995, Mazziotta et al. 2001a, Mazziotta et al. 2001b)	T1, T2, PD	---	152	---
40 th Generation MNI152	(Fonov et al. 2011)	T1, T2, PD	4.5–18.5	152	---
ICBM452	(Mazziotta et al. 2001a, Mazziotta et al. 2001b)	T1	---	452	
Volumetric parcellation					
MNI	(Collins et al. 1999, Collins et al. 1995a)	T1	---(Collins et al. 1999)	1	142
Talairach Daemon	(Lancaster et al. 1997, Lancaster et al. 2000)	---	---	---	160
Harvard-Oxford	(Caviness et al. 1996)	T1	---	37	69
Freesurfer	(Fischl et al. 2002, Fischl et al. 2004)	---	---	40	74
LPBA40	(Shattuck et al. 2008b)	T1, T2	29.20 ± 6.30	40	56
AAL	(Tzourio-Mazoyer et al. 2002)	---	---	---	45
Cytoarchitecture	(Eickhoff et al. 2005)	---	---	---	---
IBSR18	(Internet Brain Segmentation Repository 2014)	T1	7–71		84
CUMC12	(Cardviews software 2014)	T1	26–41	12	128
MGH10	(Nieto-Castanon et al. 2003)	T1	22–29	10	74
SRI24	(Rohlfing et al. 2010)	T1, T2, PD	19-84	24	56
101 labeled	(Klein, Tourville 2012)	T1, T2	---	5 + several brains from other atlases	40

These analysis will help to further understand the methodology and algorithms proposed in this PhD thesis.

III.2.2.2 Singular Points Identification

III.2.2.2.1 Introduction

The high discriminative power of feature detection and the large number of applications using features, have made descriptors a major research trend for the last decades. Some examples are in automatic product inspection, remote sensing, object recognition, image segmentation and document processing. Recently, descriptors have been increasingly used in several medical imaging applications. In this thesis, firstly descriptors have been explored as a research topic in computer vision and image processing. Then, important applications of descriptors in medical imaging applications have been reviewed, taking into account that the main medical application of the proposed research work is the identification of relevant anatomical information related to brain injury, as underlined in previous sections.

A descriptor uniquely characterizes an image in a way that allows it to be compared and/or matched to other images (Wu et al. 2000). In other words, an image descriptor is an array

of organized singular points whose features should be discriminable enough to be able to distinguish among different points as well as sufficiently stable so as not to be influenced by unexpected imaging variations. The rows of the array represent the number of detected singular points and the columns contain the location of each point and a vector of features around each singular point neighborhood.

Image descriptors can be roughly classified into global and local descriptors (Eitz et al. 2011):

A *global descriptor* describes the whole image. These type of descriptors are generally not very robust since a change in part of the image will affect the resulting descriptor. As these descriptors are easy computing and storage efficient, they are widely used, for example, by MPEG-7 descriptors (Wang, Zhang 2011).

A *local descriptor* describes a patch within an image. Multiple local descriptors are used to match an image. These type of descriptors are more robust to changes between matched images, as not all the descriptors need to match for the comparison to be made. There are two main applications of local descriptors: (i) traditional utilization (image registration (Zitová, Flusser 2003) and object recognition (Lowe 1999b)) and (ii) bag-of-features (Nowak, Jurie & Triggs 2006) and hyper-features (Agarwal, Triggs 2006). The traditional utilization involves: feature detection, feature description and feature matching, whereas the second utilization includes feature detection, feature description, feature clustering and frequency histogram construction for image representation (Li, Allinson 2008).

(Raoui et al. 2011) shows that local descriptors achieve a higher accuracy when the desired image possesses several meaningful region whereas global descriptors obtain better performance when the regions of the image does not vary significantly, like synthetic images. In most medical imaging modalities, there is a great variability among image regions. This variability combined with the goal of getting both global and quantitative indicators are the reasons why the state of the art of descriptors is focused on local descriptors on medical imaging applications.

The key stages of a descriptor algorithm, as shown in Fig.III.8, are: (1) singular point location, (2) orientation assignment and (3) singular point description (Lowe 2004a). In the first stage, the algorithm locates points whose features are different from its neighbors. In the second stage, each singular point is assigned one or more orientations point based on gradient directions. Finally, a vector of features is computed around each singular point. Thus, a singular point is characterized not only by its location but also by a vector of features of its neighborhood. In the following paragraphs, these three stages are explained in detail.

Figure III. 8 Key stages of a descriptor algorithm.

III.2.2.2.2 Singular Point Location: Types of Features and Detectors

There are several types of features attending to diverse imaging characteristics. Depending on the type of feature, there are different algorithms to detect it, known as detectors. In this section, the types of features (A) first and then the detector algorithms (B) are reviewed.

A. Types of features

As previously mentioned, singular points are those points whose intensity are different from its neighbors. These points must be reliably localized under varying image conditions, viewpoint changes and in the presence of noise (Mikolajczyk, Schmid 2005b). Singular points, also commonly called features, can be grouped into the following types: (1) color representation, (2) texture representation, (3) local features and (4) shape representation (Deselaers, Keysers & Ney 2008). Due to the specific characteristics of medical imaging studies, and more specifically to MRI studies, this review of the state of the art is focused mainly on local features.

Local features are identified based on the average changes of image intensity that result from shifting a local window (W) by a small amount (u, v) in various direction within the image (Harris, Stephens 1988a), as shown in Fig.III.9.

Figure III. 9 Window displacement to detect local features within an image.

In order to compare each pixel located inside the window, the sum of squared differences (SSD) of the intensity values before and after window displacement is computed (Eq. III. 1).

$$E(u, v) = \sum_{(x,y) \in W} [I(x + u, y + v) - I(x, y)]^2 \approx \sum_{(x,y) \in W} [I(x, y) + [I_x \ I_y] \begin{bmatrix} u \\ v \end{bmatrix} - I(x, y)]^2 \quad (\text{Eq. III.1})$$

Therefore, SSD can be rewritten as (Eq. III.2), where I_{xx} , I_{yy} and $I_x I_y$ are the second partial derivatives for each image point:

$$E(u, v) \approx [u \ v] \left(\sum_{(x,y) \in W} \begin{bmatrix} I_{xx} & I_x I_y \\ I_x I_y & I_{yy} \end{bmatrix} \right) \begin{bmatrix} u \\ v \end{bmatrix} \approx [u \ v] H \begin{bmatrix} u \\ v \end{bmatrix} \quad (\text{Eq. III.2})$$

The eigenvectors $(\tilde{x}_1, \tilde{x}_2)$ and eigenvalues (λ_1, λ_2) of the matrix H determine the type of local feature. There are four main types of features: (1) edges, (2) corners, (3) blobs and (4) ridges, as shown in Fig.III.10.

Figure III. 10 Types of features based on the eigenvectors and eigenvalues.

An edge is defined as a point where the gradient in one direction is high, while the gradient in the orthogonal direction is low (Lee). In terms of eigenvalues, a point is an edge when one of the eigenvalues is much greater than the other one. A corner is defined as a point for which there are two dominant and different edge directions in a local neighborhood of the point (Stockman, Shapiro 2001) or when λ_1 and λ_2 are large and have similar values. A blob is defined as the cross point where at least six direction gradient lines join (Stockman, Shapiro 2001) or when λ_1 and λ_2 are small. A ridge or saddle is defined as a local maximum of a real-valued function of a vector variable (Eberly et al. 1994). In terms of eigenvalues, a ridge is a point where the eigenvalues are complex numbers.

B. Feature detectors

There are several algorithms in the literature to detect these types of features, also named detectors. Firstly, this section presents the most known detector algorithms and then, a systematic review of the state of the art in the field of local features detectors in medical imaging applications.

B1) *General Algorithms*

B1.1) *Edge Detectors*

The best-known edge detector algorithm are mainly: Canny, Sobel, Roberts and Prewitt. Algorithms for edge detection contain four steps: (1) filtering, (2) enhancement, (3) detection and (4) localization, as shown in Fig.III.11. Filtering is commonly used to improve the performance of an edge detector with respect to noise. It should be taken into consideration that more filtering to reduce noise results in a loss of edge strength. Enhancement emphasizes pixels where there is a significant change in local intensity values and it is usually performed by computing the gradient magnitude. As many points in an image have a nonzero value for the gradient, and not all of these points are edges for a particular application, some method should be used to determine which points are edges. The location and orientation of an edge can be estimated with the resolution required for the application (Jain, Kasturi & Schunck).

Figure III. 11 Workflow of a general edge detector.

Canny detector (Canny 1986) runs in five main steps: smoothing, finding gradients, non-maximum suppression, double thresholdings and edge tracking by hysteresis. In this case, the enhancement stage has been divided into the finding gradients step and the non-maximum suppression. The objective of the smoothing step is to remove the image noise. In the next step, the algorithm finds regions of the image where the grayscale intensity presents the maximum variation through the gradients of the image. Only local maxima in the gradient image are preserved whereas the other regions are deleted. Potential edges are determined by double thresholdings. From these potential edges, only those pixels that are connected to strong edge are selected. This detector is the first derivative of a Gaussian and it approximates the operator that optimizes the product of signal-to-noise ratio and localization

Roberts cross operator (Roberts 1963) provides a simple approximation to the gradient magnitude in order to highlight regions of high spatial frequency which often correspond to edges. The operator consists of a pair of 2x2 convolution kernels in each orientation (Gx and Gy), as shown in Fig.III.12.

Gx		Gy	
1	0	0	-1
0	-1	1	0

Figure III. 12 Masks for the Roberts cross operator.

These kernels are designed to respond maximally to edges running at 45° to the pixel grid and can be applied separately to the image (Maini, Aggarwal). The absolute magnitude of the gradient is computed by combining the two masks.

Sobel operator (Danielsson, Seger 1990) consists of a pair of 3x3 convolution kernels, as shown in Fig.III.13.

Gx			Gy		
-1	0	+1	+1	+2	+1
-2	0	+2	0	0	0
-1	0	+1	-1	-2	-1

Figure III. 13 Masks for the Sobel operator.

Sobel kernels respond maximally to edges running vertically and horizontally, in other words, there is one kernel for each of the two perpendicular orientations. As in the previous case, the absolute magnitude is obtained by combining the two masks.

Prewitt filter (Prewitt 1970) is used to detect edges based on applying a vertical and horizontal filter as the Sobel operator, as shown in Fig.III.14. The main difference from Sobel filter is that Prewitt operator does not place any emphasis on pixels that are closer to the center of the masks.

Gx			Gy		
-1	0	+1	+1	+1	+1
-1	0	+1	0	0	0
-1	0	+1	-1	-1	-1

Figure III. 14 Masks for the Prewitt filter.

Marr-Hildreth algorithm (Marr, Hildreth 1980) is based on the Laplacian operator. This operator searches for zero crossings in the second derivative of the image to find edges, thus it highlights regions of rapid intensity change. Two commonly used discrete approximations to the Laplacian filter are shown in Fig.III.15.

0	-1	0	-1	-1	-1
-1	4	-1	-1	8	-1
0	-1	0	-1	-1	-1

Figure III. 15 Examples of masks for the Marr-Hildreth filter.

Scharr operator (Scharr 1999) improves the estimation of gradient orientation by optimizing the gradient estimation in the Fourier domain. Fig.III.16 shows the Scharr masks. This operator is recognized as more accurate than Sobel.

$1/16 *$	-3	0	3	$1/16 *$	-3	-10	-3
	-10	0	10		0	0	0
	-3	0	3		3	10	3

Figure III. 16 Examples of masks for the Scharr operator.

The Kirsch operator (Kirsch 1971) takes a single kernel mask and rotates it in 45 degree increments through all 8 compass directions, as shown in Fig.III.17. The maximum magnitude across all directions is considered as an edge.

0°	-1	-1	-1	-1	-1	0	45°
	0	0	0	-1	0	1	
	1	1	1	0	1	1	
90°	-1	0	1	0	1	1	135°
	-1	0	1	-1	0	1	
	-1	0	1	-1	-1	0	

Figure III. 17. Examples of masks for the Kirsch operator.

Fig.III.18 shows the result of applying some of these detector algorithms to a T1w MRI image. This figure illustrates that not all these algorithms are applicable to a MRI study due to the intrinsic properties of this medical imaging modality.

Figure III. 18. Example of results of some general descriptor algorithms.

B1.2) Corner Detectors

The workflow of corner detectors is similar to the workflow of edge detectors shown in Fig.III.7.

Harris detector (Harris, Stephens 1988b) is a popular technique to detect corners due to its strong invariance to rotation, scale, illumination variation and image noise (Schmid, Mohr & Bauckhage 2000). This detector is based on the local autocorrelation function of a signal, which measures the local changes of the signal with patches shifted by a small amount in different directions (Sipiran, Bustos 2011). Using a Taylor expansion of the local autocorrelation and then truncating it to the first order terms to approximate the shifted image, the Eq. III. 3 is obtained:

$$e(x, y) = S \begin{bmatrix} \sum_{xi,yi} W I_x^2 & \sum_{xi,yi} W I_x I_y \\ \sum_{xi,yi} W I_x I_y & \sum_{xi,yi} W I_y^2 \end{bmatrix} S^T = SE(x, y) S^T \quad (\text{Eq. III.3})$$

Where $S = [\Delta x \ \Delta y]$ is a shift vector, I_x and I_y denote the partial derivatives in x and y , and W is the windows used to evaluate the matrix E in (x_i, y_i) points. The matrix E contains enough local information related to the neighborhood structure. In order to avoid the eigenvalue calculation, each pixel in the image is assigned $h(x, y)$ (Eq. III.4) with k constant.

$$h(x, y) = \det(E) - k(\text{tr}(E))^2 \quad (\text{Eq. III.4})$$

SUSAN detector (Smith, Brady 1997) stands for 'smallest univalue segment assimilating nucleus'. This detector is based on a circular mask over the pixel to be tested located at $\bar{r}_0$, also named nucleus, the rest of the pixels in this mask are represented by $\bar{r}$. Every pixel is compared to the nucleus using a function that has the appearance of a smoothed rectangular function as in Eq.III.5, where I is the brightness of the pixel, t determines the radius and the power of the exponent has been determined empirically. The area of the USAN (n) is given by Eq. III. 6.

$$c(\bar{r}) = e^{-\left(\frac{I(\bar{r}) - I(\bar{r}_0)}{t}\right)^6} \quad (\text{Eq. III.5})$$

$$n(\bar{r}_0) = \sum_{\bar{r}} c(\bar{r}, \bar{r}_0) \quad (\text{Eq. III.6})$$

Then n is compared with a fixed threshold g , which is set to $3n_{\max}/4$, where $n_{\max}$ is the maximum value which n can take. The response of the SUSAN operator is given by Eq.III.7. Therefore, SUSAN operator only has a positive score if the area is small enough.

$$R(M) = \begin{cases} g - n(M) & \text{if } n(M) < g \\ 0 & \text{otherwise} \end{cases} \quad (\text{Eq. III.7})$$

The value of g determines the minimum size of the univalue segment. If g is large enough, then this becomes an edge detector. For corner detection, two more steps are necessary: (i) to find the centroid of the SUSAN, a corner will have the centroid far from the nucleus and (ii) all points on the line from the nucleus through the centroid out to the edge of the mask are in the SUSAN.

Shi-Tomas corner detector (Shi, Tomasi 1994), also known as Kande-Tomasi corner detector, is based on the Harris detector. Shi-Tomas detector computes the minimum of absolute values of the eigenvalues due to the fact that under certain assumptions, the corners are more stable for tracking.

FAST corner detector (Rosten, Drummond 2006) stands for ‘features for accelerated segment test’. This detector performs two test. Firstly, candidate points are identified by applying a segment test to every pixel within the image. The test is passed, if n contiguous pixels, on a Bresenham circle of radius r , are darker than $I_p - t$, or brighter than $I_p + t$, where I_p is the brightness of the investigated pixel p and t is a threshold value. As the first test produces many adjacent responses around the interest point, additional criterion is applied to perform a non-maximum suppression. This allows for precise feature localization.

Laplacian of Gaussian (LoG) (Marr, Hildreth 1980) combines Gaussian filtering and the Laplacian. The main characteristics of the LoG are: (1) the smoothing filter is a Gaussian, (2) the enhancement step is the second derivative: the Laplacian in two dimensions, (3) the detection criterion is the presence of a zero crossing in the second derivative with a corresponding large peak in the first derivative and (4) the location of features can be estimated with subpixel resolution using linear interpolation. The 2D LoG function centered at zero and with Gaussian standard deviation σ has the form of Fig.III.19 and the definition as in Eq. III. 8.

$$LoG(x, y) = -\frac{1}{\pi\sigma^4} \left[1 - \frac{x^2 + y^2}{2\sigma^2} \right] e^{-\frac{x^2 + y^2}{2\sigma^2}} \quad (\text{Eq. III.8})$$

Figure III. 19 Laplacian of Gaussian

Difference of Gaussians (DoG) (Lowe 2004b) performs two different Gaussian filters with different radius. DoG is a good approximation for the LoG and much faster to compute. The main purpose of this detector is to identify locations that are invariant to scale change of the image, and hence, it searches for stable features across all possible scales, using a continuous function of scale known as scale-space (Witkin 1984). In order to identify stable point locations in scale space, the difference of two nearby scales separated by a constant multiplicative factor k is computed (Eq.III.9).

$$D(x, y, \sigma) = (G(x, y, k\sigma) - G(x, y, \sigma)) * I(x, y) \quad (\text{Eq.III.9})$$

Where $I(x, y)$ is the input image, $G(x, y, \sigma)$ is a variable-scale Gaussian and $*$ represents the convolution.

B1.3) Blob Detectors

The determinant of the Hessian (Lindeberg 1998) of a function $f(x, y)$ is defined as in Eq.III.10, where f_{xx} , f_{yy} , f_{xy} and f_{yx} are the second partials derivatives.

$$H(x, y) = f_{xx}(x, y)f_{yy}(x, y) - f_{xy}(x, y)f_{yx}(x, y) \quad (\text{Eq.III.10})$$

If $f(x, y)$ has continuous second partial derivatives and $f_x(x_0, y_0)=0$ and $f_y(x_0, y_0)=0$, then:

- $H > 0$ and $f_{xx}(x_0, y_0) > 0$ implies (x_0, y_0) is a local minimum and thus a blob.
- $H > 0$ and $f_{xx}(x_0, y_0) < 0$ implies (x_0, y_0) is a local maximum and also a blob.
- $H < 0$ implies (x_0, y_0) is a saddle or ridge point.
- $H = 0$, (x_0, y_0) cannot be classified.

MSER (Matas et al. 2004) stands for 'maximally stable extremal regions'. It is used as a method of blob detection in images. This detector considers the set of all possible thresholdings of an intensity image, I , to a binary image E . A maximally stable extremal region is then a connected region in E with little size change across several thresholdings. The number of thresholds for which the region is stable is called the margin of the region.

B1.4) Ridge Detectors

PCBR detector (Hongli Deng et al. 2007) stands for ‘principle curvature-based region detector’. This detector obtains the principal curvature from the Hessian matrix, the local maximum of principal curvature values are used to define the identified regions. The principal curvature images are cleaned by a morphological closing and eigenvector-flow guided hysteresis thresholding. Then, traditional watershed algorithm is applied on images to acquire regions. Stable regions are selected across local scale changes. This detector mainly identifies ridge features.

Kadir-Brady saliency detector (Kadir, Brady 2001) extracts features of objects in images that are distinct and representative. This detector applies a global threshold to the image and it chooses the highest salient point in the saliency-space. Each region must be sufficiently distant from all others to qualify as a separate entity.

B1.5) Analysis and Conclusions

In conclusion, table III.5 summarizes the reviewed feature detector algorithms, the type of feature each algorithm detects and the field of application. Most of the algorithms are wide used on computer vision applications, but there is growing trend towards using them on image analysis applications including medical ones.

Table III. 5 Summary table of general descriptor algorithms.

Feature Detector	Reference	Type of Feature				Application
		Edge	Corner	Blob	Ridge	
Canny	(Canny 1986)					Computer Vision, Image analysis
Roberts	(Roberts 1963)					Computer Vision, Image analysis
Sobel	(Danielsson, Seger 1990)					Computer Vision, Image analysis
Prewitt	(Prewitt 1970)					Computer Vision, Image analysis
Marr-Hildreth	(Marr, Hildreth 1980)					Computer Vision, Image analysis
Scharr	(Scharr 1999)					Computer Vision, Image analysis
Kirsch operator	(Kirsch 1971)					Medical images
Harris	(Harris, Stephens 1988b)					Computer Vision, Image analysis
SUSAN	(Smith, Brady 1997)					Computer Vision, Image analysis
Shi and Tomasi	(Shi, Tomasi 1994)					Computer Vision, Image analysis
FAST	(Rosten, Drummond 2006)					Computer Vision, Image analysis
Laplacian of Gaussian (LoG)	(Marr, Hildreth 1980)					Computer Vision, Image analysis

Difference of Gaussians (DoG)	(Lowe 2004b)					Computer Vision, Image analysis
Determinant of Hessian	(Lindeberg 1998)					Computer Vision, Image analysis
MSER	(Matas et al. 2004)					Computer Vision, Image analysis
PCBR	(Hongli Deng et al. 2007)					Computer Vision, Image analysis
Kadir-Brady	(Kadir, Brady 2001)					Computer Vision

B2) Algorithms Used in Medical Imaging Applications

A systematic review of the state of the art in the field of local features detectors in neuroimaging applications is presented. Search of the literature was performed using *Web of Science (WOS)*. Key words employed were: ‘local feature detector’, ‘medical imaging’, ‘from 2009 to present’. As shown in Fig.III.20, there is an increasing number of citations per year of research papers describing detector algorithms applying to medical imaging applications.

Figure III. 20 Citations in each year of detector algorithms on medical imaging applications. Source: Web of Science (WOS: <http://apps.webofknowledge.com/>)

Table III.6 summarizes the reviewed research papers. It shows the type of detector algorithm used, its medical imaging application and the anatomical region where the algorithm is applied. As it can be observed, these algorithms are used in many different anatomical regions to segment regions of interest.

Table III. 6 Example of detector algorithms used in medical imaging applications

Detector	Application	Imaging Modalities	Anatomical Structure	Reference
Canny	Shape Reconstruction	X-ray	Leg	(Baka et al. 2011)
	Segmentation	CT	Leg	(Rathnayaka et al. 2011)
	Registration	US	Prostate	(Pan et al. 2011)

	Segmentation	Microscopic images	Female reproductive system	(Bergmeir, Garcia Silvente & Manuel Benitez 2012)
LoG	Nodule measurement	CT	Lung	(Diciotti et al. 2010)
	Segmentation	US	Breast	(Bocchi, Rogai 2011)
	Lesion detection	Retinographies	Eye	(Fazlollahi et al. 2013)
DoG	Reconstruction of volumetric US	US	Liver	(Ni et al. 2009b)
	Medical image retrieval	CT	Thorax	(Haas et al. 2012a)
	Segmentation	Endoscopic	Colon	(Tamaki et al. 2013)
MSER	Segmentation	MRI	Hearth	(Abdelfadeel, ElShehaby & Abougabal 2014)
	Segmentation	MRI	Fetal brain	(Keraudren et al. 2014)
	Segmentation	CT	Kidney	(Jianfei Liu et al. 2015)

III.2.2.2.3 Orientation Assignment

As previously mentioned, the goal of this stage is to assign a consistent orientation to each singular point based on local image properties. In this section, six orientation assignment methods have been reviewed based on: (1) intensity differences (Taylor, Drummond 2011), (2) gradient histogram (Lowe 2004a)(Bay et al. 2008), (3) Haar wavelets (Bay et al. 2008), (4) smoothed gradient (Brown, Szeliski & Winder 2005), (5) center of mass (Gauglitz, Turk & Höllerer 2011) and (6) histogram of intensities (Gauglitz, Turk & Höllerer 2011) (see Fig. III.11).

(Taylor, Drummond 2011) compute the orientation based on intensity differences of eight pairs of pixels within a circle around the singular point location. Each of the eight vectors, corresponding to these eight differences, is scaled by the intensity difference between the respective two points. These vectors are concatenated and the direction of the resulting vector determines the final singular point orientation. This method is extremely fast but it is susceptible to image noise and assumes existence of strong intensity differences in a relatively small neighborhood.

(Lowe 2004a) calculate the gradient orientation at each point within a region around the singular point. A histogram is computed based on the gradient orientation weighted by the strength of the local gradient and a Gaussian around the singular point. The highest peak in this histogram and the peaks whose value is higher than 80% of the highest peak are refined by fitting a parabola to the histogram values around the respective location. They are finally taken as the orientations of the singular points.

(Bay et al. 2008) obtain the orientation by convoluting the image with two first-order Haar wavelets. The filter responses at certain sampling points around the singular point are represented as a vector in a two-dimensional space. Finally, a sliding window of $\pi/3$ is used to sum up all vectors within its range and the longest vector determines the orientation.

(Brown, Szeliski & Winder 2005) take the orientation from the local gradient of the image previously smoothed with a Gaussian filter ($G(\mu, \sigma)$). The orientation is calculated as in Eq.III.11, where I is the image at the singular point location (x_r, y_r) . A large σ ensures smooth variation of gradients across the image and thus a certain robustness to error in the singular point location. However, the cost of this method increases quadratically with σ .

$$\theta_r = \arctan(\nabla(G * I(x_r, y_r))) \quad (\text{Eq.III.11})$$

(Gauglitz, Turk & Höllerer 2011) propose to consider a circular neighborhood R around the singular point (x_r, y_r) and to compute the sum as in Eq.III.12. Where $r = \|(x, y) - (x_r, y_r)\|$, $w(r) = 1 - (r/r_{max})^2$ is a radial weighting function, $S = \sum w(r) \cdot I(x, y) \cdot (c_x, c_y)$ is the “center of mass” of the neighborhood if each pixel’s intensity is interpreted as its “mass”. The orientation relative to the singular point location is a function of the local intensities.

$$(c_x, c_y) = \frac{1}{S} \sum w(r) ((x, y) - (x_r, y_r)) I(x, y) \quad (\text{Eq.III.12})$$

Histogram of intensities (Gauglitz, Turk & Höllerer 2011) is a combination of the “center of mass” concept and the gradient histogram. Each pixel (x, y) in a region R around the singular point (x_r, y_r) is entered into a histogram based on the angle $\theta(x, y) = \arctan(y - y_r, x - x_r)$ between the two points, weighted by its intensity $I(x, y)$ and a radial weighting function $w(\|(x, y) - (x_r, y_r)\|)$. From this histogram, each peak above a certain threshold is accepted as the singular point location and refined by quadratic interpolation.

Figure III. 21 Orientation assignment. A) (Taylor, Drummond 2011) Intensity differences method. B) (Lowe 2004a) Gradient histogram. C) (Bay et al. 2008) Haar wavelets.

III.2.2.2.4 Singular Point Descriptor

In this stage, the goal is to organize the information extracted from previous stages. This information is organized on a matrix structure, where each row represents a singular point and each column contains different information not only relative to the singular point but also to its neighborhood. The most common information stored in each column is the spatial location of the point and intensity information of its neighborhood.

Many approaches have been proposed for extracting and organizing singular points. As previously mentioned, the analysis of the state of the art of descriptors is focused on local descriptors. This section follows the same organization as in the one above. First, a state of the art of descriptors algorithms has been done. Then, some important applications of descriptors in medical imaging applications have been reviewed.

It is important to describe the *scale-space* concept in the first place. As many of the reviewed descriptors are invariant to scaling, a ‘tool’ for analyzing images at different scales is

implemented. This tool is the scale-space (Lindeberg 1994), the idea is to embed the original image into a one-parameter family of gradually smoothed images, in which the fine scale details are successively suppressed. Scale-space resembles receptive field profiles registered in neurophysiological studies of the mammalian retina and visual cortex (Young 1987).

A. General Descriptor Algorithms

Table III.7 summarizes the reviewed algorithms. It specifies how each algorithm perform the three main stages: (i) singular point location, (ii) orientation assignment and (iii) singular point descriptor.

Table III. 7 Descriptor algorithms.

Algorithm	Singular Point Location	Orientation Assignment	Reference
SIFT	DoG	Gradient histogram	(Lowe 1999a)
PCA-SIFT	DoG	Local gradients maps	(Yan Ke, Sukthankar 2004)
HOG	DoG	Gradient	(Dalal, Triggs 2005)
GLOH	DoG	Gradient histogram and PCA	(Mikolajczyk, Schmid 2005a)
RIFT	DoG	Local gradients	(Skelly, Sclaroff 2007)
SURF	Determinant of Hessian	Haar wavelets	(Bay et al. 2008)
CenSurE	Harris	None	(Agrawal, Konolige & Blas 2008)
LESH	---	Gabor filter	(Sarfraz, Hellwich 2008)
BRIEF	Corners, but it does not specify any detector	None.	(Calonder et al. 2010)
BRISK	FAST	Comparing gradients of long pairs.	(Leutenegger, Chli & Siegwart 2011)
ORB	FAST, Harris	Moments	(Rublee et al. 2011)
FREAK	FAST	Comparing gradients of preselected 45 pairs.	(Alahi, Ortiz & Vanderghenst 2012)
G-SURF	Determinant of Hessian	Gabor	(Alcantarilla, Bergasa & Davison 2013)

‘Scale Invariant Feature Transform’ (SIFT) descriptor (Lowe 2004b) extracts features invariant to image translation, scaling and rotation, and partially invariant to illumination changes and affine projections. The input image is convolved with two Gaussian functions with different smoothing and then subtracting. Singular points are defined as maxima and minima of the result of the DoG operators, being DoG an approximation of LoG and less costly computationally speaking. Maxima and minima are determined by comparing each point in the scale-space to its eight neighbors at the same level of scale-space. A point is compared to its 8 neighbors at the same level of scale-space as well as its nine neighbors in next and previous scales (see Fig.III.12). If it is a local extreme, it is a singular point.

Figure III. 22 SIFT: scale-space concept (Lowe 2004b)

The method used to assign an orientation is the gradient histogram, described above. Once the orientation is computed, a 16x16 neighborhood around the singular point is taken. It is divided into 16 sub-blocks of 4x4 size. For each sub-block, 8 bin orientation histogram is created. Thus, a total of 128 bin values per detected singular point is stored in each row of the descriptor.

'PCA-SIFT' (Yan Ke, Sukthankar 2004) is an alternative approach to SIFT descriptor. It computes local maps of the gradient magnitude over local patches around singular points. The local patch for each singular point is warped to a scale normalized 39x39 reference frame common to all singular points. These patches are then oriented with respect to a dominant image orientation to achieve rotational invariance. These local gradient maps are projected to a lower-dimensional subspace using principal component analysis (PCA). For each singular point, the gradient map is computed, and after contrast normalization, projected to the lower dimensional subspace.

'Histograms of oriented gradients' (HOG) descriptor (Dalal, Triggs 2005) is based on a set of gradient orientation histograms computed over a grid in the image domain. In contrast to SIFT descriptor, HOG is considered a regional image descriptor. HOG is closely related to the regional receptive field histograms defined over sub-regions in the image domain. The main differences between HOG and SIFT, also based on a set of gradient orientation histograms, are: (i) HOG includes a dependency on image positions, as it is composed of a set of smaller histograms defined over sub-regions and (ii) HOG is defined from gradient orientations instead of partial derivatives. There are two versions of HOG: R-HOG, where local histograms are computed over a rectangular grid and C-HOG where the histograms are computed over a circular grid.

'Gradient Location and Orientation Histogram' (GLOH) descriptor (Mikolajczyk, Schmid 2005a) is based on SIFT descriptor, in other words, it is also a local position-dependent histogram of gradient orientations around a singular point. The main differences are: (i) it is computed over a log-polar grid instead of over a rectangular grid, (ii) it uses a larger number of 16 bins for quantizing the gradient directions whereas SIFT uses 8 bins and (iii) it uses principal component analysis to reduce the dimensionality of the image descriptor.

'Rotation Invariant Feature Transform' (RIFT) descriptor (Skelly, Sclaroff 2007) is based on SIFT algorithm, and hence the detector is DoG. In order to achieve rotation invariance, the

position and orientation of each neighboring point is determined by the local gradients. The orientation is based on the gradient histogram method.

'Speed Up Robust Feature Transform' (SURF) descriptor (Bay et al. 2008) approximates LoG with box filters, as shown in Fig.III.14.A. This algorithm computes the cumulative distribution of image intensity values, also known as integral image, and it uses the determinant of the Hessian to find blob-like structures. Scale-space is analyzed by up-scaling the filter size.

The orientation of each landmark is based on Haar wavelets. The dominant orientation is estimated by calculating the sum of all responses within a sliding orientation window of angle 60 degrees, as shown in Fig.III.14.B.

Figure III. 23 SURF. A) Approximation of LoG with box filters. B) Orientation assignment (Bay et al. 2008)

SURF descriptor has 64 columns per each detected singular point, as a neighborhood of size $20\sigma \times 20\sigma$ is taken around the singular point, where σ is the scale in which the point has been detected. This region is divided into 4×4 sub-regions. For each sub-region, horizontal and vertical wavelet responses are taken.

'Center Surround Extremas' (CenSurE) descriptor (Agrawal, Konolige & Blas 2008) identifies singular points by computing at the extreme of the center-surround filters over multiple scales, using the original image resolution for each scale. Points that are either maxima or minima in this neighborhood are the singular point locations. This descriptor does not compute the orientation of each singular point.

'Local energy based shape histogram' (LESH) descriptor (Sarfraz, Hellwich 2008) is based on local energy models of feature perception. These models are based on the energy response in terms of local filter orientations into a compact spatial histogram. In order to detect singular points in images with a high reliability in presence of illumination and noise, the image is convolved with a bank of Gabor wavelets kernels tuned to five spatial frequencies and eight orientations.

'Binary robust independent elementary features' (BRIEF) descriptor (Calonder et al. 2010) uses simple binary test between pixels in a smoothed image patch. BRIEF, unlike SURF, does not compute any orientation. One important point to take into account is that BRIEF is a feature descriptor, this means that BRIEF does not provide any method to find the features.

'Binary robust invariant scalable keypoints' (BRISK) descriptor (Leutenegger, Chli & Siegwart 2011) identifies singular points based on the FAST detector. BRISK descriptor is composed as a binary string by concatenating the results of simple brightness comparison tests. The key concept of this descriptor is that it makes use of a pattern used for sampling the neighborhood of the singular point. This descriptor relies on an easily configurable circular sampling pattern from which it computes brightness comparisons to form a binary descriptor string.

'Oriented FAST and Rotated BRIEF' (ORB) (Rublee et al. 2011) detector is a fusion of FAST detector and BRIEF descriptor with modifications to improve the performance. First, it uses FAST to find singular points, then it applies the Harris corner measure to find the top singular points among the points detected with FAST. In order to compute the orientation, this descriptor computes the intensity weighted centroid of the patch with located corner at center. The direction of the vector from this corner point to centroid gives the orientation. It uses machine learning techniques to learn the optimal set of sampling pairs.

'Fast retina keypoint' (FREAK) descriptor (Alahi, Ortiz & Vanderghenst 2012) is similar to BRISK, hence it is based on patterns, and to ORB, since it also uses machine learning techniques. Whereas BRIEF uses random pairs, ORB uses learned pairs and BRISK uses a circular pattern where points are equally spaced on circles concentric. FREAK uses the retinal sampling grid which is also circular with the difference of having higher density of points near the center. Each sampling point is smoothed with a Gaussian kernel where the radius of the circle represents the size of the standard deviation of the kernel. As previously mentioned, this descriptor follows ORB's approach and it tries to learn the pairs by maximizing variance of the pairs and taking pairs that are not correlated. The first pairs selected mainly compare sampling points in the outer rings of the pattern whilst the last pairs compare mainly points in the inner rings of the pattern. This is similar to the way the human eye operates. With the aim of compensating rotation changes, it measures the orientation of the singular point and rotates the sampling pairs by measure angle, similar to BRISK. But FREAK uses a predefined set of 45 symmetric sampling pairs.

'Gauge-SURF' (G-SURF) descriptor (Alcantarilla, Bergasa & Davison 2013) is a variant of SURF based on second-order multi-scale gauge derivatives. G-SURF derivatives are evaluated relative to the gradient direction at every pixel, whereas SURF derivatives are all relative to a single chosen orientation. It describes each pixel in the image in such way that the descriptor is the same even in the image is rotated.

B. Medical Imaging Descriptor Algorithms

A systematic review of the state of the art in the field of descriptors in medical imaging applications is presented. Search of the literature was performed using *IEEEExplore* and *Google Scholar* public databases. Key words employed were: 'descriptor', 'medical imaging', 'from 2010 to present'.

In medical imaging applications, descriptor algorithms are commonly used in (1) registration algorithms, (2) content-based image retrieval systems (CBIR), (3) anatomical region detection, (4) model generation and (5) segmentation. The most used medical imaging modality are CT and MRI, as shown in Table III.8. Regarding the anatomical regions where this type of algorithms are commonly applied, these are the abdominal and the brain.

Table III. 8 Medical imaging descriptor algorithms.

Application	Detector	Anatomical Region	Imaging Modalities	Reference
Registration	SURF	Abdominal	CT	(Lukashevich, Zalesky & Ablameyko 2011b)
	SURF	Brain	PET and MRI	(Wang et al. 2010)

	SURF	Brain	MRI	(Gu et al. 2014)
	DoG	General	CT	(Liang Li, Zhiqiang Chen & Yijie Wang 2012)
	Harris and LoG	Liver	CT	(Ying Cao et al. 2010)
	SURF	Lung	CT	(Yang, Xie 2013)
	SIFT	Brain	MRI	(Sunyeong Kim, Yu-Wing Tai 2014)
	SIFT	Gynecologic	Colposcopy	(Meslouhi et al. 2010)
	SIFT	Liver	CT	(Shaohua Su, Yan Sun 2011)
	SURF	Lung	CT	(Han 2010)
	SIFT	Eye	Retinal images	(Ghassabi et al. 2013)
	SURF	Abdominal	WCE	(Spyrou, Iakovidis 2012)
	Based on LoG, Harris	Abdominal	Video	(Yip et al. 2012)
	SIFT	Brain	CT	(Paganelli et al. 2013)
CBIR	DoG	Abdominal	X-Ray	(Yimo Tao et al. 2011)
	Shi and Tomasi	Brain	MRI	(Unay, Ekin & Jasinski 2010)
	SURF	General	X-Ray	(Amaral et al. 2010)
	SIFT	General	CT	(Haas et al. 2012b)
	SIFT	Brain (tumor)	MRI	(Gharbi, Marzouki 2013)
	SIFT	Carcinoma image	CT	(Wang et al. 2011)
	DoG	Breast	X-Ray	(Al-Shamlan, El-Zaart 2010)
	SURF	General(Wojnar, Pinheiro 2012)	X-Ray	(Wojnar, Pinheiro 2012)
Anatomical Region detection	DoG	Brain	T1 - MRI	(Toews et al. 2010)
	SIFT, SURF and RIFT	Brain	MRI	(Razlighi, Stern 2011)
	SURF	General	CT	(- Feulner et al. - 2009)
	SURF	General	CT	(Feulner et al. 2011)
	Based on Harris and LoG	Microscopic images	Microscopic images	(Zhang, Wu & Bennett 2014)
	SIFT	Abdominal	Video	(Kamencay et al. 2013)
	SIFT	Brain	MRI	(Keraudren et al. 2013)
Model Generation	LoG	Abdominal	WCE images	(Yichen Fan, Meng & Baopu Li 2010)
	SURF	Pelvis	CT	(Kamencay et al. 2014)
	SURF	Vertebra	X-Ray	(Jun-Hui Gong et al. 2012)
	SIFT and SURF	Abdominal	Endoscopic video	(Sargent et al. 2009)
Segmentation	Based on LoG and DoG	Brain	CT	(Shuzhi Ye, Sheng Zheng & Wei Hao 2010)
	SUSAN	Brain	CT	(Wenhong Sun et al. 2011)

	Canny and texture	Brain	MRI	(Somkantha, Theera-Umpun & Auephanwiriyaikul 2011)
	Canny	Brain	T1 - MRI	(Sarathi et al. 2013)
	Determinant of Hessian and DoG	Eye	US	(Pires et al. 2013)
	Harris, Shi and Tomasi and FAST	General	US	(Zukal et al. 2013)
	LoG	Skin	Clinical skin images	(Jaseema Yasmin, Sathik & Beevi 2011)
	SIFT	Breast	X-Ray	(Liasis, Pattichis & Petroudi 2012)
	BRIEF	Lung	CT	(Ng et al. 2014)
	SURF	Blood	Microscopy	(Bicao Li, Keke Shang & Yu Zheng 2011)
	SURF	Eye	Fundus Images(Adal et al. 2013)	(Adal et al. 2013)
	SIFT	Lung	CT	(Frag et al. 2010)
	SIFT	Brain	MRI	(Mizotin et al. 2012)
	SIFT	Prostate	MRI	(Meijuan Yang et al. 2013)

III.2.2.2.5 Analysis and Conclusions

In this section, algorithms related to the identification of singular points on images have been reviewed. In order to fully understand these algorithms, a review of the different types of features on images have been performed first. Features can be classified into color, texture, local and shape. The specific characteristics of medical imaging studies (gray-scale intensity images) makes local features the most common type as they are identified based on the average changes of image intensity.

The most used descriptors in the applications described in the state of the art are scale-invariant feature transform (SIFT) (Lowe 2004a) and speeded up robust features (SURF) (Bay et al. 2008). Table III.9 shows the main application of these two algorithms.

Table III. 9 Main application of SURF and SIFT

	Thorax	Brain	Eye	Gynecologic	General	Oncology
SIFT	(Shaohua Su, Yan Sun 2011)	(Sunyeong Kim, Yu-Wing Tai 2014)	(Ghassabi et al. 2013)	(Meslouhi et al. 2010)	(Liang Li, Zhiqiang Chen & Yijie Wang 2012)	(Wang et al. 2011)
SURF	(Lukashevich, Zalesky & Ablameyko 2011b)	(Wang et al. 2010, Jayachandran, Ekin & De Haan 2012, Lukashevich, Zalesky & Ablameyko 2011b)	(Adal et al. 2013)		(Amaral et al. 2010)	

		Ablameyko 2011a)				
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However, these two algorithms are invariant to linear intensity changes whereas medical images, such as CT or MRI, involving non-linear changes do not work properly on medical video-endoscopic images, since these type of images present different characteristics than those of the computer vision applications (Sargent et al. 2009). Thus, these algorithms may be adapted to be used on a medical context, whether in surgical video applications or in medical applications using medical images such as CT or MRI.

III.2.2.3 Registration

III.2.2.3.1 Introduction

The goal of an image registration algorithm is to find the optimal transformation that best aligns two different images, in this case, two different brains. Image registration is a crucial step for image analysis. In particular, in this PhD, registration is the key stage to automatically delineate anatomical structures that may be injured. The method described in this research work addresses a key need in the management of brain injury, that was identified by (Irimia et al. 2012): “[...] *the key methodological hurdle that must be overcome in order to make structural neuroimaging a powerful tool for predicting TBI outcome is the current paucity of automated image processing methods that can allow researchers to analyze large numbers of TBI CT/MRI volumes without the need for excessive user input or intervention.*”

Fig.III.21 shows the diagram of a typical registration algorithm. The image that remains unchanged is named *reference* image, the image that will be transformed to be as similar as possible to the reference image is known as *source*. This diagram usually consists of four main parts: (1) the geometric transformation trying to optimize a certain similarity measure when applied to the source image; (2) the similarity measure, also known as the cost function, measuring how much the ‘registered’ image looks like the reference one; (3) the optimizer looks for the best similarity search strategy until the similarity measure or the number iterations reach a threshold; and (4) the interpolator resamples the voxel intensity of the ‘registered’ image into the new coordinate system based on the geometric transformation.

Figure III. 24 Diagram of a typical registration algorithm.

Table III.10 shows a classification of medical image registration algorithms proposed by (Maintz, Viergever 1998). There are several classification criteria attending to: dimensionality, nature of the registration bases, nature of the transformation, domain of transformation, interaction, optimization procedure, modalities involved, subject and anatomical region. This classification will help us to classify the type of algorithms proposed in this PhD.

Table III. 10 Classification of medical image registration algorithms proposed by (Maintz, Viergever 1998).

Classification Criteria		Divisions	
Dimensionality	Spatial dimension: 2D/2D, 2D/3D, 3D/3D		
	Temporal series		
Nature of the registration basis	Extrinsic (based on foreign objects introduced into the image space)	Invasive	Stereotactic frame
			Fiducials
		Non-invasive	Anatomical
			Geometrical
	Intrinsic (based on the patient)	Landmark based	Anatomical
			Geometrical
		Segmentation based	Rigid models (curves, surfaces, volumes)
			Deformable models (snakes, nets)
		Voxel property based	Reduction to scalars/vectors
			Using full image content
Non-image based (calibrated coordinate systems)			
Nature of transformation	Rigid (only rotation and translations)		
	Affine (translation, rotations, scaling and shearing)		

	Projective	
	Curved	
Domain of transformation	Local	
	Global	
Interaction	Interactive	Initialization supplied
		No initialization supplied
	Semi-automatic	User initializing
		User correcting
		Both
	Automatic	
Optimization procedure	Parameters computed (the transformation parameters are computed directly)	
	Parameters searched for (the transformation parameters are computed using optimization algorithms)	
Modalities involved	Monomodal	
	Multimodal (CT/MRI, CT/PET, CT/SPECT, PET/MRI, MRI/US, etc.)	
	Modality to model	
	Patient to modality (to align the patient with the coordinate system of the equipment)	
Subject	Intra-subject	
	Inter-subject	
	Atlas	
Anatomical region	Head	
	Thorax	
	Abdomen	
	Limbs	
	Pelvis	
	Spine and vertebrae	

According to (Oliveira, Tavares 2014), several reviews on image registration algorithms can be found in the literature such as: general medical imaging registration (Hajnal, Hill 2001, Hill et al. 2001, Goshtasby 2005, Fischer, Modersitzki 2008, Slomka, Baum 2009) and reviews focusing on specific anatomical regions such as: cardiac (Makela et al. 2002); breast (Guo et al. 2006); retina (Laliberté, Gagnon & Sheng 2003) and brain (Klein et al. 2009, West et al. 1997, Yangming Ou et al. 2014, Hellier et al. 2003, Yanovsky et al. 2009, Yassa, Stark 2009, Christensen et al. 2006, Song et al. 2010, Klein et al. 2010, Ardekani et al. 2005a). As it can be verified, the state of the art in registration algorithms could be as extensive as wanted. In order to focus on the review, only medical registration algorithms whose major application is on neuroimaging applications are analyzed.

III.2.2.3.2 Registration on Neuroimaging

(Yassa, Stark 2009) evaluated the performance of twelve registration algorithms applied to align with the medial temporal lobe (MTL) based on: AFNI (Cox 1996), SPM5 (W. D. Penny et

al. 2007), LDDMM ('Large deformation diffeomorphic mapping') (Beg et al. 2005, Miller et al. 2005), DARTEL (W. D. Penny et al. 2007), Demons (Vercauteren et al. 2007). They showed that these algorithms improve the results when they are applied on a region of interest. This solution is far from the objective we aim to obtain: a global registration algorithm. Registration algorithms are only applied on imaging studies of healthy individuals.

Klein et al. (Klein et al. 2009) evaluated fourteen non-linear deformation algorithms applied to human brain registration. This paper classifies registration algorithms into linear (rigid and affine) and non-linear. In particular, it compares AIR ('automatic image registration') (Woods et al. 1998), ANIMAL (Collins et al. 1995), ART ('Automatic registration toolbox') (Ardekani et al. 2005b), Diffeomorphic Demons (Vercauteren et al. 2009a), FNIRT (Jenkinson et al. 2002), IRTK ('Image registration toolkit') (Schnabel et al. 2001), JRD-fluid ('Jensen-Rényi Divergence') (Ming-Chang Chiang et al. 2006), ROMEO ('Robust multilevel elastic registration based on optical flow') (Hellier, Morandi & Naucziciel 2012), SICLE ('inverse-consistent linear-elastic') (Christensen, Johnson 2001), SyN 'symmetric image normalization method' (Avants et al. 2008b), and four different SPM5 algorithms (W. D. Penny et al. 2007) ('SPM2-type', regular Normalization, Unified Segmentation, and DARTEL). ART, SyN, IRTK and Dartel gave the best results according to overlap and distance measures.

In a later paper, (Klein et al. 2010) compared some of the most accurate volume registration methods, 'automatic registration toolbox' (ART) (Collins et al. 1995b, Kjemis et al. 1999, Kosugi et al. 1993) and 'symmetric image normalization method' (SyN) (Avants et al. 2008b), with other surface registration methods, as FreeSurfer (<http://surfer.nmr.mgh.harvard.edu/>) (Ardekani et al. 2005b) and Spherical Demons (Yeo et al. 2010).

(Yangming Ou et al. 2014) compared twelve registration algorithms: FLIRT (Jenkinson, Smith 2001), AIR (Woods et al. 1998), ART (Ardekani et al. 2005b), ANTs ('Advanced Normalization Tools') (Avants et al. 2008a), Demons (Thirion 1998), Diffeomorphic Demons (Vercauteren et al. 2009b), DRAMMS ('Deformable registration via attribute matching and mutual-saliency weighting') (Ou et al. 2011), DROP ('Dense image registration through MRFs and efficient linear programming') (Glocker et al. 2008), CC-FFD ('Correlation coefficient - Free form deformation') (Rueckert et al. 1999), ('Mutual information - Free form deformation') MI-FFD (Rueckert et al. 1999), ('Sum of squared difference - Free form deformation') SSD-FFD (Rueckert et al. 1999), FNIRT (Jenkinson et al. 2002). These algorithms have been tested with normal subject databases such as LPBA40 or IBSR and with Alzheimer imaging studies from ADNI database and imaging studies of patients with recurrent brain tumors. They concluded that DRAMMS and ANTs gained relatively higher accuracy in skull-stripped images, followed by ART, Demons, DROP and FFD. DRAMMS showed a relatively higher accuracy when raw, multi-site or pathology data were involved.

Although there are different registration algorithms, there are still some challenges to be resolved. As shown in (Yangming Ou et al. 2014) main challenges in inter-subject brain MRI registration are: (1) inter-subject anatomical variability; (2) intensity Inhomogeneity, noise and structural difference in raw images; (3) protocol and FOV differences in multi-site databases; and (4) pathology-induced missing correspondences in lesion images. The reviewed algorithms

have not been applied on imaging studies of patients affected from stroke or TBI. The main reason for this is that most of these algorithms are intensity-based and due to the fact that brain lesions introduce intensity abnormalities, these algorithms do not work properly.

Hence, in the last years there have been an increasing interest in developing registration algorithms specifically applied to brain injury, restricting this term to TBI and stroke, as a cause of the great health and social impact of the impairments associated to both of them. (Zagorchev et al. 2011) presented a methodology to identify structural biomarkers in brain MRI studies. In particular, they proposed a shape-constrained deformable model of the brainstem, putamen, thalamus and caudate. They obtained promising results regarding the adaptation of the model of these structures. However, they did not obtain an integral biomarker taking into account more anatomical structures. (Lou et al. 2013) proposed a deformable registration algorithm based on the Bhattachayya distance. Although they introduced interesting ideas in the same direction to the ones proposed in this PhD, the computed transformation is not often well defined in regions where hemorrhage or edema occur since they introduce high intensity variations. (Glatz et al. 2015) has recently proposed a method to label basal ganglia on MRI, showing that labeling brain structures are still to be resolved and hence, the remaining need for designing and developing algorithms to identify anatomical structures on brain studies. (Ledig et al. 2015) presented a framework for the robust and fully-automatic delineation of brain MRI with gross changes in anatomy, named (MALP-EM) ‘Multi-atlas label propagation with expectation-maximization based refinement’. This research work suggested the spatially weighted combination of probabilistic labeling results obtained through different techniques into a common segmentation exploiting individual benefits. As it will be explained later, the combination of spatial information with intensity-based information is one of the basis of this PhD.

To sum-up, the main ideas of the registration algorithms reviewed up to here are: (1) TBI and stroke lesions introduce topological differences associated with intensity abnormalities and/or location alterations; (2) most of the registration algorithms are intensity-based and it has to be taken into account that these differences become a great obstacle for image registration algorithms based only on intensity imaging parameters; (3) there are few registration algorithms specially designed for these type of lesions, mainly due to the fact that most of them do not work properly when intensity varies; (4) in the last five years, there have been an increasingly interest in the development of new registration algorithms to help clinicians in the difficult task of improving and personalizing as much as possible rehabilitation treatments; and (5) spatial information is important to improve the registration around lesion areas. Therefore, one of the main proposals of this PhD is a registration algorithm based on features. Since the final goal is to identify anatomical structures which may be injured, the use of atlases is essential. Atlas propagation techniques rely on the accurate registration of the atlas and the MRI study to determine the spatial transformation of the atlas labels into the target space, that will be the control subject or patient space. This can be difficult if the target image differs from the available atlases due to the presence of pathology. In order to identify weaknesses of existing landmark-based registration algorithms used on brain applications, in the next paragraphs the state of this type of algorithms is reviewed.

III.2.2.3.3 Landmark-Based Registration Algorithms on Brain

As shown in Table III. 10, registration algorithms can be classified into (1) landmark based, (2) segmentation based and (3) voxel property based according to the intrinsic nature of the registration basis. In particular, as indicated above, this section is focused on landmark-based registration algorithms, also known as feature-based registration algorithms. This type of methods establishes a correspondence between a set of especially distinct points on both images. Based on this correspondence, a geometrical transformation is computed to map the source images to the reference images. Fig.III.22 shows the typical workflow of a landmark-based registration algorithm.

Figure III. 25 Workflow of a general landmark-based registration algorithm. Feature extraction corresponds to the Section III.2.2.2.

The reminder of this section is organized as follows: first, we review different feature matching techniques and then, a review of the state of the art of landmark-based registration algorithm is presented.

Feature Matching

Feature matching can be defined as the process to find corresponding interest points between a pair of images based on the similarity or a ‘distance’ measure. The ‘distance’ among features or landmarks to be matched is based on their particular characteristics (Oliveira, Tavares 2014). According to (Cha 2007) this distance can be classified into eight main syntactic families of distances: (1) L_p Minkowski; (2) L_1 ; (3) intersection; (4) inner product; (5) squared-chord; (6) squared L_2 ; (7) Shannon’s entropy and (8) combinations.

Table III. 11 Distances for feature matching

Algorithm	Equation	Reference
L_p Minkowski family		
Euclidean L_2	$d_{\text{Euc}} = \sqrt{\sum_{i=1}^d P_i - Q_i ^2}$	(Krause 1986)

City block L_1	$d_{CB} = \sum_{i=1}^d P_i - Q_i $	(Krause 1986)
Minkowski L_p	$d_{Mk} = \sqrt[p]{\sum_{i=1}^d P_i - Q_i ^p}$	(Krause 1986)
Chebyshev L_∞	$d_{Cheb} = \max_i P_i - Q_i $	(Van Der Heijden et al. 2005)
L_1 family		
Sorensen	$d_{sor} = \frac{\sum_{i=1}^d P_i - Q_i }{\sum_{i=1}^d P_i + Q_i }$	(Sorensen 1948)
Gower	$d_{gow} = \frac{1}{d} \sum_{i=1}^d P_i - Q_i $	(Gower 1971)
Soergel	$d_{sg} = \frac{\sum_{i=1}^d P_i - Q_i }{\sum_{i=1}^d \max(P_i, Q_i)}$	(Monev 2004)
Kulczynski	$d_{kul} = \frac{\sum_{i=1}^d P_i - Q_i }{\sum_{i=1}^d \min(P_i, Q_i)}$	(Monev 2004)
Canberra	$d_{can} = \frac{\sum_{i=1}^d P_i - Q_i }{\sum_{i=1}^d P_i + Q_i}$	(Gordon 1999)
Lorentzian	$d_{lor} = \sum_{i=1}^d \ln(1 + P_i - Q_i)$	(Deza, Deza 2009)
Intersection family		
Intersection	$d_{IS} = \sum_{i=1}^d \min(P_i, Q_i)$	(Duda, Hart & Stork 2012)
Wave hedges	$d_{WH} = \sum_{i=1}^d \frac{ P_i - Q_i }{\max(P_i, Q_i)}$	(Hedges 1976)
Czekanowski	$d_{Cze} = \frac{\sum_{i=1}^d P_i - Q_i }{\sum_{i=1}^d (P_i + Q_i)}$	(Gordon 1999)
Motyka	$d_{Mot} = \frac{\sum_{i=1}^d \max(P_i, Q_i)}{\sum_{i=1}^d (P_i + Q_i)}$	(Deza, Deza 2009)
Kulczynski	$d_{Kul} = \frac{\sum_{i=1}^d \min(P_i, Q_i)}{\sum_{i=1}^d P_i - Q_i }$	(Deza, 2009)
Ruzicka	$S_{Ruz} = \frac{\sum_{i=1}^d \min(P_i, Q_i)}{\sum_{i=1}^d \max(P_i, Q_i)}$	(Deza, 2009)
Tani-moto	$d_{Tani} = \frac{\sum_{i=1}^d (\max(P_i, Q_i) - \min(P_i, Q_i))}{\sum_{i=1}^d \max(P_i, Q_i)}$	(Duda, Hart & Stork 2012)
Inner product family		
Harmonic mean	$S_{HM} = 2 \sum_{i=1}^d \frac{P_i Q_i}{P_i + Q_i}$	(Deza, 2009)
Cosine	$S_{cos} = \frac{\sum_{i=1}^d P_i Q_i}{\sqrt{\sum_{i=1}^d P_i^2} \sqrt{\sum_{i=1}^d Q_i^2}}$	(Deza, 2009)
Jaccard	$d_{Jac} = \frac{\sum_{i=1}^d (P_i - Q_i)^2}{\sqrt{\sum_{i=1}^d P_i^2 + \sum_{i=1}^d Q_i^2} - \sqrt{\sum_{i=1}^d P_i Q_i}}$	(Kumar, Hassebrook 1990)
Dice	$d_{Dice} = \frac{\sum_{i=1}^d (P_i - Q_i)^2}{\sqrt{\sum_{i=1}^d P_i^2 + \sum_{i=1}^d Q_i^2}}$	(Dice 1945)
Squared-chord family		
Bhattacharyya	$d_B = -\ln \sum_{i=1}^d \sqrt{P_i Q_i}$	(Deza, Deza 2009)
Hellinger	$d_H = 2 \sqrt{1 - \sum_{i=1}^d \sqrt{P_i Q_i}}$	(Deza, Deza 2009)
Matusita	$d_M = \sqrt{2 - 2 \sum_{i=1}^d \sqrt{P_i Q_i}}$	(Matusita 1955)
Squared-chord	$d_{sqc} = \sum_{i=1}^d (\sqrt{P_i} - \sqrt{Q_i})^2$	(Gavin et al. 2003)
Squared L_2 family		
Squared Euclidean	$d_{sqe} = \sum_{i=1}^d (P_i - Q_i)^2$	(Deza, Deza 2009)
Pearson χ^2	$d_p = \sum_{i=1}^d \frac{(P_i - Q_i)^2}{Q_i}$	(Barnard 1992)
Neyman χ^2	$d_N = \sum_{i=1}^d \frac{(P_i - Q_i)^2}{P_i}$	(Barnard 1992)

Squared χ^2	$d_{sq\chi^2} = \sum_{i=1}^d \frac{(P_i - Q_i)^2}{P_i + Q_i}$	(Gavin et al. 2003)
Probabilistic symmetric χ^2	$d_{p\chi^2} = \sum_{i=1}^d \frac{(P_i - Q_i)^2}{P_i}$	(Barnard 1992)
Divergence	$d_{Div} = 2 \sum_{i=1}^d \frac{(P_i - Q_i)^2}{(P_i + Q_i)^2}$	(Deza, Deza 2009)
Clark	$d_{Clk} = \sqrt{\sum_{i=1}^d \left(\frac{ P_i - Q_i }{P_i + Q_i} \right)^2}$	(Deza, Deza 2009)
Additive symmetric χ^2	$d_{Ad\chi^2} = \sum_{i=1}^d \frac{(P_i - Q_i)^2 (P_i + Q_i)}{P_i Q_i}$	(Deza, Deza 2009)
Shannon's entropy family		
Kullback – Leibler	$d_{KL} = \sum_{i=1}^d P_i \ln \frac{P_i}{Q_i}$	(Kullback, Leibler 1951)
Jeffreys	$d_J = \sum_{i=1}^d (P_i - Q_i) \ln \frac{P_i}{Q_i}$	(Jeffreys 1946)
K divergence	$d_{Kdiv} = \sum_{i=1}^d P_i \ln \frac{2P_i}{P_i + Q_i}$	(Jeffreys 1946)
Topsoe	$d_{top} = \sum_{i=1}^d \left(P_i \ln \left(\frac{2P_i}{P_i + Q_i} \right) + Q_i \ln \left(\frac{2Q_i}{P_i + Q_i} \right) \right)$	(Deza, Deza 2009)
Jensen-Shannon	$d_{JS} = \frac{1}{2} \left[\sum_{i=1}^d \left(P_i \ln \left(\frac{2P_i}{P_i + Q_i} \right) + Q_i \ln \left(\frac{2Q_i}{P_i + Q_i} \right) \right) \right]$	(Deza, Deza 2009)
Jensen difference	$d_{JD} = \sum_{i=1}^d \left[\frac{P_i \ln P_i + Q_i \ln Q_i}{2} - \left(\frac{P_i + Q_i}{2} \right) \ln \left(\frac{P_i + Q_i}{2} \right) \right]$	(Deza, Deza 2009)
Combination		
Taneja	$d_{TJ} = \sum_{i=1}^d \left(\frac{P_i + Q_i}{2} \right) \ln \frac{P_i + Q_i}{2\sqrt{P_i Q_i}}$	(Taneja 1995)
Kumar-Johnson	$d_{KJ} = \sum_{i=1}^d \frac{(P_i^2 - Q_i^2)^2}{2(P_i Q_i)^{\frac{3}{2}}}$	(Kumar, Johnson 2005)
Avg(L_1, L_∞)	$d_{ACC} = \frac{\sum_{i=1}^d P_i - Q_i + \max P_i - Q_i }{2}$	(Deza, Deza 2009)

Geometric Transformation

Regarding the strategies to select the nearest points in order to compute the geometric transformation, the most widely used algorithm is the kd-tree, which is quite useful in low-dimensional data, but quickly loses its effectiveness as dimensionality increases (Friedman, Bentley & Finkel 1977). (Arya et al. 1998) imposed a bound on the accuracy of the kd-tree method and proposed the use of a priority queue to speed up the search in a tree by visiting tree nodes in order of their distance from the query point. (Silpa-Anan, Hartley 2008) proposed the use of multiple randomized kd-trees as a means to speed up the search of nearest-neighbor. (Liu et al. 2004) presented a new metric tree, named spill-tree, this metric allows an overlap between the children of each node. (Mikolajczyk, Matas 2007) evaluated several tree structures, including kd-tree, hierarchical k-means tree and the agglomerative tree.

According to the distance metric and the strategy to select the nearest point, different registration algorithms applied on different brain imaging applications have been developed. (Rohr et al. 2000) proposed an algorithm based on approximating thin-plate splines to compute an elastic transformation on a region of interest that has been automatically identified. (Pennec, Ayache & Thirion 2000) presented a method to extract reliable differential geometry features (crest lines and extremal points) from 3D images and several rigid registration algorithms to put into correspondence these features in two different images and to compute the rigid transformation between them.

(Rohr et al. 2001) proposed a semi-automatic approach to the localization of 3-D anatomical point landmarks and an elastic image registration algorithm. (Johnson, Christensen 2002) proposed a registration algorithm based on both landmark and intensity information by estimating the forward and reverse transformation between two images while minimizing the inverse consistency error.

(Joshi et al. 2007) described a method for registration that also produces an accurate one-to-one point correspondence between cortical surfaces. This is achieved by first parameterizing and aligning the cortical surfaces using sulcal landmarks by using a constrained harmonic mapping to extend this surface correspondence to the entire cortical volume. Finally, this mapping is refined using an intensity-based warping algorithm.

(Lui et al. 2010) described optimized conformal parameterizations which match landmark curves exactly with shape-based correspondences between them and they proposed a method to minimize a compound energy functional that measures the harmonic energy of the parameterization maps and the shape dissimilarity between mapped points on the landmark curves.

(Kurkure et al. 2011) proposed a method for landmark-constrained, intensity-based registration without determining landmark correspondences a priori. The proposed method performs dense image registration and identifies the landmark correspondences, simultaneously, using a single higher-order Markov Random Field model.

(Liu et al. 2012) developed a technique to automate landmark selection for point-based interpolating transformations for nonlinear medical image registration. Point landmarks are placed at regular intervals on contours of anatomical features, and their positions are optimized along the contour surface by a function composed of curvature similarity and displacements of the homologous landmarks. (Guerrero et al. 2012) proposed the use of descriptors that define a landmark based on the structural pattern of its neighborhood.

(Wan et al. 2013) introduced a method to estimate optimal landmark configurations. An important landmark configuration that will be used as a training landmark set was learned for an image pair with a known deformation. This landmark configuration can be considered as a collection of discrete points. A generic transformation matrix between a pair of training landmark sets with different deformation locations was computed via an iterative close point (ICP) alignment technique.

(Han et al. 2014) proposed a landmark detection method for robust establishment of correspondences between subjects. Firstly, they annotate distinctive landmarks in the training images. Then, they use regression forest to simultaneously learn the optimal set of features to best characterize each landmark and the non-linear mappings from local patch appearances of image points to their displacements towards each landmark. (Lui et al. 2014) proposed an efficient iterative algorithm, called the quasi-conformal (QC) iteration, to compute the T-Map. The basic idea is to represent the set of diffeomorphisms using Beltrami coefficients (BCs) and look for an optimal BC associated to the desired T-Map.

(Jiang et al. 2015) presented a novel anatomy-guided landmark discovery framework that defines and optimizes landmarks via integrating rich anatomical, morphological, and fiber connectional information for landmark initialization, group-wise optimization and prediction, which are formulated and solved as an energy minimization problem. They used functional neuroimaging studies such as DTI and fMRI.

III.2.2.3.4 Analysis and Conclusions

In this section we have first reviewed the state of the art of registration algorithms used to identify brain injury, restricting the term brain injury to lesions associated to stroke and TBI. Table III.12 sums up the main registration algorithms applied on neuroimaging applications.

Table III. 12 Summary of registration algorithms on neuroimaging

	Deformation	Brain Injury	Linear vs Non-linear	Reference
LDDMM	Diffeomorphic	No	NL	(Beg et al. 2005, Miller et al. 2005)
Demons	Demons	No	NL	(Vercauteren et al. 2007)
AFNI	3D rotation and translation	No	L	(Cox 1996)
AIR	5 th order polynomial warps	No	NL	(Woods et al. 1998)
ANIMAL	Local translations	No	NL	(Collins et al. 1995)
ART	Non-parametric, homeomorphic	No	NL	(Ardekani et al. 2005b)
Diffeomorphic Demons	Non-parametric, diffeomorphic	No	NL	(Vercauteren et al. 2009a)
FNIRT	Cubic B-splines	Yes (DTI)	NL	(Jenkinson et al. 2002)
IRTK	Cubic B-splines	No	NL	(Schnabel et al. 2001)
JRD-fluid	Viscous fluid	No	NL	(Ming-Chang Chiang et al. 2006)
ROMEO	Local affine	No	NL	(Hellier, Morandi & Naucziciel 2012)
SICLE	Diffeomorphic	No	NL	(Christensen, Johnson 2001)
SyN	Diffeomorphic	No	NL	(Avants et al. 2008b)
SPM2-type	Discrete cosine transforms	No	NL	(W. D. Penny et al. 2007)
Regular Normalization	Discrete cosine transforms	No	NL	(W. D. Penny et al. 2007)
Unified Segmentation	Discrete cosine transforms	No	NL	(W. D. Penny et al. 2007)
DARTEL	Finite difference model	No	NL	(W. D. Penny et al. 2007)
ANTs	Symmetric velocity	No	L	(Avants et al. 2008a)
DRAMMS	Cubic B-splines	No	NL	(Ou et al. 2011)

DROP	Cubic B-splines	No	L	(Glocker et al. 2008)
CC-FFD	Cubic B-splines	No	NL	(Rueckert et al. 1999)
MI-FFD	Cubic B-splines	No	NL	(Rueckert et al. 1999)
SSD-FFD	Cubic B-splines	No	NL	(Rueckert et al. 1999)
FLIRT	Affine	No	L	(Jenkinson, Smith 2001)
Deformable registration via the Bhattacharyya distance	Viscous fluid model	Yes (TBI)	NL	(Lou et al. 2013)
Shape-constrained deformable model	EM based	Yes (TBI)	NL	(Ledig et al. 2015)

As it can be seen in this chart, there are barely registration algorithms used to identify anatomical structures affected by brain injury. Most of these algorithms are intensity based, so they do not work properly when a patient suffers from TBI or stroke, as it origins intensity abnormalities. Therefore, it is necessary to develop algorithms that take into account not only intensity-based features but also spatial location information. Moreover, the need to use atlas to identify those anatomical structures featuring high probability of being affected after a brain injury event, leads our research towards feature-based registration algorithms. That is the main reason why we include the state of the art on this type of registration algorithms. Table III.13 summarizes the reviewed algorithms. In particular, the summary takes into account the metric or transformation applied; if it requires the intervention of the user to select or correct some landmarks (semi-automatic); the type of information used to identify landmarks and compute the similarity among them; the area of the brain engaged in the transformation; the imaging modality and if the algorithms has ever been applied on TBI or stroke imaging.

Table III. 13 Summary of reviewed landmark-based registration algorithms

Algorithm	Distance-Metric-Transformation	Automatic	Type of information	Local or Global	Imaging modality	TBI-stroke	Reference
Project imagine	Navier Equation	Semi-automatic	Intensity based	Local	MR/CT	No	(Rohr et al. 2000)
Differential Geometry	Iterative closest point (ICP)	Automatic	Intensity based	Global	CT	No	(Pennec, Ayache & Thirion 2000)
Thin-Plate splines (TPS)	Euclidean	Semi-automatic	Intensity based	Local	MRI	No	(Rohr et al. 2001)
Consistent landmark and intensity registration algorithm	TPS	Automatic	Intensity based	Global	MRI	No	(Johnson, Christensen 2002)
Surface-constrained	Harmonic mapping	Automatic	Intensity based	Global	MRI	No	(Joshi et al. 2007)
Surface registration with shape-	Diffeomorphism based on energies.	Automatic	Intensity based	Local and global	---	No	(Lui et al. 2010)

based landmark matching							
Deformable registration of gene expression data	Markov Random Field model	Automatic	---	Global	---	No	(Kurkure et al. 2011)
Local curvature for point-based nonlinear registration	Euclidean	Automatic	Intensity based	Global (based on curves)	MRI	No	(Liu et al. 2012)
Local self-similarities	Self-similarity	Automatic	Structural pattern	Local	MRI	No	(Guerrero et al. 2012)
Learning optimal landmark configurations	ICP – Euclidean distance	Automatic	Intensity based	Local	MRI	No	(Wan et al. 2013)
Robust anatomical landmark detection	Regression forest	Automatic	Intensity based (Training set)	Local	MRI	No	(Han et al. 2014)
Teichmüller Mapping (T-Map)	Diffeomorphism using Beltrami coefficients	Automatic	Intensity based	Global	---	No	(Lui et al. 2014)
A-DICCOL	Euclidean – principal curvature	Automatic	Intensity based	Local	DTI-fMRI	No	(Jiang et al. 2015)

As it can be noticed, none of these reviewed algorithms have been applied on TBI or stroke imaging studies. The main reason is that most of them are intensity based algorithms, so the main information taken into account to compute the geometrical transformation is the intensity. As it has been previously mentioned, one of the main characteristics of TBI and stroke is the perturbation of intensity levels both in the affected and in the surrounding area. These intensity changes make these algorithms not to work properly. Hence, when these imaging studies are compared to atlases there are not enough information to identify areas with high probability of being injured. Moreover, most landmark-based registration algorithms assume that a small deformation is sufficient to register a set of images. This state is not true when there are lesions associated to some strokes and TBI which can affect great and disperse areas. In this PhD, we propose an algorithm that takes into account not only intensity information but also spatial information, as it will be explained later.

III.2.2.4 Brain Lesion Detection

Several methods aimed to detect tumors or lesions associated with neurodegenerative diseases have been presented in recent years. However, the algorithms that have been developed for lesion detection on TBI and stroke are less numerous. Most of these algorithms are based on segmentation methods (Stamatakis, Tyler 2005); (Shen, Szameitat & Sterr 2008, Seghier et al. 2008a, Senyukova et al. 2011, Kruggel, Paul & Gertz 2008b, de Boer et al. 2009b, Bianchi et al. 2014a) or methods for extracting biomarkers (Bo Wang et al. 2013). Almost all of

the previous research works use T1 and/or T2 magnetic resonance imaging (MRI) studies. The goal of most of these papers is to detect injured white matter or lesions in concrete functional areas such as the Broca's area. Nevertheless, it is important to point out that no research works have been found whose final objective is the automated detection of injured anatomical structures on medical imaging associated with brain injury.

Previous works have concluded that pathological changes on anatomical structures are always associated with intensity abnormalities and/or location alterations (Joel Ramirez, Fu Quiang Gao, Sandra E. Black 2008). Therefore, the combination of both intensity and location information can help develop a deeper knowledge on the complex brain structure-function relations on brain injury (Wei et al. 2002, Ramirez, Gao & Black 2008).

One of the biggest research group working on the characterization of traumatic brain injury is the one of Professor Van Horn of the UCLA. This group is made up of important and well-known researchers of the University of Utah, Harvard Medical School, University of North Carolina, Georgia Tech and Boston University. They are working on a project named 'Driving Biological Project on Traumatic Brain Injury', whose key directions are: quantitative measurements of TBI using new research tools; user-supervised, efficient, smart, flexible analysis, registration and parcellation; and dynamic 3D imaging with multivariate information over time. Until now, we have found neither a methodology nor algorithms whose goal was exactly the detection of anatomical lesions on structural MRI studies. Since most of the research works only identify lesions on functional areas and do not detect the underlying anatomical structures.

Nowadays, one of the main challenges of neurorehabilitation is to establish objective parameters in order not only to personalize and design evidence-based therapies but also to evaluate these treatments. Moreover, there is an increasing interest in imaging modalities such as 'Diffusion tensor imaging' (DTI) to identify paths that could explain the relation structure-function. Therefore, the development of new algorithms to identify anatomical structures featuring high injured probability may help both to improve the current neurorehabilitation treatments and to identify 'hubs' (anatomical structures) in a wired structure where 'paths' are the physical connections among them.

III.3. Neuroimaging Software Tools

As previously mentioned, one of the most relevant direct applications of the contributions of this PhD is to integrate the proposed algorithms into a neuroimaging software tools. Table III.14 includes the most known neuroimaging software tools.

Table III. 14 Summary of neuroimaging software tools.

Tool	Segmentation	Registration	Functional or Structural	Imaging Modality	Brain Injury	Free Software	Comments	Reference
3D Slicer	Yes	Yes	Both	All	Yes	Yes	- Multiple applications - Multiple anatomical locations	(Steve Pieper, Ron Kikinis 2012)
aidScans	Yes	No	Structural	CT/MRI	Only tumors	No	- Brain tumors - Different anatomical locations	(Any Intelli 2015)
Amira	Yes	Yes	Structural	CT/MRI	No	No	- Multiple application areas	(Stalling, Westerhoff & Hege 2005)
AFNI	Yes	Yes	Functional	fMRI	No	Yes	- Mapping human brain activity.	(NIMH SSCC - Scientific and Statistical Computing Core 2015)
Analyze	Yes	Yes	Both	CT/MRI/PET	No	No	- Multiple anatomical locations	(AnalyzeDirect 2015)
Bioimage Suite	Yes	Yes	Both	CT/MRI	Yes	No	- Multiple anatomical locations.	(Yale University 2015)
BrainMagix	Yes	Yes	Both	CT/MRI/PET	Yes	No	- Biomarker software for clinical trials	(imagilys 2015)
BrainSuite	Yes	Yes	Structural	MRI	No	No	- Extraction of the inner and outer surface of the cortex	(Bhushan et al.)
BrainVISA	Yes	Yes	Structural	MRI	No	No	- Surface analysis	(UNATI 2013)
BrainVoyager	Yes	Yes	Both	MRI/fMRI	No	No	- Visualization of brain images.	(Brain Innovation 2015)

							- It combines MEG and EEG data	
Tool	Segmentation	Registration	Functional or structural	Imaging modality	Brain injury	Free software	- Comments	Reference
CamBA	Yes	Yes	Functional	fMRI	No	No	- It is used in the department of psychiatry	(University of Cambridge 2015)
Camino	No	Yes	Functional	DTI	Yes	No	- It is used for diffusion MRI processing	(University College London 2015)
Caret	Yes	Yes	Both	MRI	No	No	- Cortex analysis	(Washington University School of Medicine 2013)
CONN	Yes	No	Functional	fMRI	No	Yes	- Display and analysis of fMRI	(Whitfield-Gabrieli, Nieto-Castanon 2012)
ExploreDTI	Yes	Yes	Functional	DTI	No	No	- DTI, fiber tractography	(Leemans et al. 2009)
FMRIB	Yes	Yes	Both	MRI	No	No	- Also known as FSL. - Structural, diffusion, functional	(Analysis Group Oxford 2015)
FMRLAB	Yes	Yes	Functional	fMRI	No	Yes	- fMRI data analysis using independent component analysis (ICA)	(Swartz center for computational neuroscience 2015)
FreeSurfer	Yes	Yes	Structural	MRI	No	No	- Analysis of cerebral cortex	(Athinoula A. Martinos Center for Biomedical Imaging 2015)
ISAS	Yes	Yes	Functional	SPECT	No	Yes	- Epilepsy surgery planning	(Yale 2015)

Mango	Yes	No	Structural	MRI	No	No	- Viewer for medical research images	(Lancaster, Martinez 2015)
Tool	Segmentation	Registration	Functional or structural	Imaging modality	Brain injury	Free software	- Comments	Reference
MIPAV	Yes	Yes	Both	CT/MRI/PET	No	No	- Commonly used to study cells and generate 3D confocal microscopy data sets.	(NIH Center for information technology 2012)
MRicro	Yes	Yes	Functional	fMRI	No	No	- Functional analysis	(University of South Carolina 2015)
MRtrix	Yes	No	Functional	DTI	No	No	- To perform and analyze DTI in the presence of crossing fibers	(Tournier 2012)
MRVision	Yes	Yes	Both	CT/MRI/fMRI	No	No	- General analysis sw.	(MRVision)
NeuroLens	Yes	Yes	Functional	fMRI	No	No	- Analysis and visualization of functional images.	(Neurolens 2015)
Olea Medical	Yes	Yes	Structural	CT and MRI	No	No	- Different anatomical locations.	(Olea Medical 2015)
PyMVPA	Yes	No	Both	CT and MRI	No	Yes	- Statistical analysis	(Hanke et al. 2009)
SDM	No	No	Functional	fMRI, DTI, PET	No	No	- Statistical analysis for meta-analyzing studies.	(Radua et al. 2012)
SPM	Yes	Yes	Both	MRI, fMRI, MEG	Yes	Yes	- Statistical studies of functional studies	(Wellcome Trust Centre for Neuroimaging 2015)

As it can be observed, most of these tools include both registration and segmentation algorithms and most of them are proprietary software. However, we do not have found a neuroimaging software tool focusing on the identification of brain lesions associated to brain injury, just as there are specific tools for epilepsy (Yale 2015) or tumors (Any Intelli 2015).

III.4. Neuroimaging Databases

The increase in the use of digital technologies in the field of health, not only regarding clinical history but also medical test such as the different medical imaging modalities, has led to a growing interest on how to organize and interact with the complex medical databases. Until few years ago, these different types of information were only used to extract data to diagnose each patient. The different clinical cases increased the experience of a determined specialist, instead of generating knowledge to be used for other specialist in order to infer precise prognoses and to improve the diagnoses in the future.

Moreover, neuroimaging research, according to (Van Horn, Toga 2014), is data intensive, multimodal and collaborative. Van Horn et al considered neuroimaging as an example of discovery-oriented science, since patterns of brain structure and activity presented across multiple subjects can be systematically extracted, examined and resulting in new knowledge. However, the infrastructure needed for supporting this advancing form of brain research is still maturing. Next steps for the development of the resources and this infrastructure require the further creation of new tools and services for data discovery, integration, analysis and visualization.

For this reason, the algorithms proposed in this PhD may help to develop tools useful not only for designing but also for recovering imaging studies from databases, as the imaging information extracted with these algorithms can be used as metadata to uniquely identify an imaging volume study.

Table III.15 summarizes the current neuroimaging databases. Most of these databases are for general brain applications and only three of them are for particular diagnosis cases. There are two databases trying to collect neuroimaging information to develop integral research programs related to brain injury and stroke. However, the access to these databases is not public so far, and only registered users can download data. Hopefully, in future years, the access to these valuable data will be open to anyone.

Table III. 15 Summary of neuroimaging databases (Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC) 2015)

ADNI	Brain scape	Brain VISA	BraVa	FITBIR: Federal Interagency Traumatic Brain Injury Research	Function al Imaging BIRN	HCP Harvard/ MGH- UCLA	HCP WU- Minn Consortiu m	Human Imaging Database (HID)	INCF	Internet Brain Volume Databas e (IBVD)	Mouse Connectome Project (MCP)	Neuro Synth	Neu roV ault	NIH Pediatric MRI Data Repository	PDBP: Parkinson's Disease Biomarkers Program
License															
ADNI	---	CeCill v2	---	NIH Data Access Policy	---	BSD/MIT- Style Open Source	---	BIRN	---	---	LONI Software	Open Softwa re 3.0	---	---	NIH Data Access Policy
---	---	---	---	---	---	LONI Software	---	BSD	---	---	---	---	---	---	---
---	---	---	---	---	---	Public Domain	---	---	---	---	---	---	---	---	---
Diagnosis															
Alzheim er Disease	---	---	Stroke	Brain Injuries	---	---	---	---	---	---	---	---	---	---	---
Domain															
Clinical Neuroinf ormatics	MRI	EEG/ MEG/ ECoG	MRI	Clinical Neuroinformati cs	MRI	EEG/MEG /ECoG	Domain Independ ent	CT	Clinical Neuroinfor matics	CT	Microscopy	MR	MR	Clinical Neuroinform atics	Clinical Neuroinformatics
Imaging Genomic s	---	MRI	---	MRI	---	Imaging Genomics	EEG/MEG /ECoG	MRI	Computati onal Neuroscie nce	MRI	MRI	PET/SP ECT	PET /SP ECT	MR	MR
MRI	---	---	---	---	---	MRI	Imaging Genomics	PET/SPECT	EEG/MEG/ ECoG	---	---	---	---	---	---
PET/SPEC T	---	---	---	---	---	---	MRI	---	MRI	---	---	---	---	---	---
Environment															
Web	We b	KDE	Web	Web	---	Web	Other	Web	Web	Web	Web	Web	We b	Web	Web
Natural Language															
EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN
---	---	FR	---	---	---	---	---	---	---	---	---	---	---	---	---
Programming Language															

---	---	C++	---	---	C++	C++	C++	Java	---	PHP	Java	---	Python	---	---
---	---	Python	---	---	csh/tcsh	Java	---	JavaScript	---	---	JavaScript	---	---	---	---
---	---	---	---	---	JavaScript	MATLAB	---	---	---	---	---	---	---	---	---
---	---	---	---	---	PL/SQL	Unix Shell	---	---	---	---	---	---	---	---	---
---	---	---	---	---	Python	---	---	---	---	---	---	---	---	---	---
---	---	---	---	---	Tcl/Tk	---	---	---	---	---	---	---	---	---	---
Supported Data Format															
ANALYZE	DICOM	ANALYZE	Other	---	ANALYZE	ANALYZE	CIFTI	Other	---	---	ANALYZE	NiftI-1	NiftI-1	DICOM	---
DICOM	---	DICOM	---	---	DICOM	DICOM	DICOM	---	---	---	Other	---	---	MINC	---
NiftI-1	---	GiftI	---	---	NiftI-1	NiftI-1	GiftI	---	---	---	---	---	---	MINC2	---
Other	---	MINC	---	---	---	Other	NiftI-1	---	---	---	---	---	---	NiftI-1	---
---	---	NiftI-1	---	---	---	---	---	---	---	---	---	---	---	---	---
---	---	Other	---	---	---	---	---	---	---	---	---	---	---	---	---

IV Materials and Methods

In which, first, the materials used in this PhD are described, and then, the methodology and algorithms proposed to analyze medical imaging studies for identifying potentially injured anatomical structures are briefly described.

<"To know the brain... is equivalent to ascertaining the material course of thought and will, to discovering the intimate history of life in its perpetual duel with external forces" – Santiago Ramón y Cajal>

IV.1. Materials

IV.1.1. Introduction

This section describes the materials used to develop this PhD. In particular, we detail which medical imaging studies are used both in the development stages as in the testing stage and the development tools used to implement the proposed algorithms.

IV.1.2. Medical Imaging Studies

In order to carry out the assessment of the proposed algorithms, we have used on the one hand, medical imaging studies of control subjects and medical imaging studies of TBI and stroke patients on the other. Although most of the implemented algorithms can be applied on different MRI acquisition sequences such as T1w, T2w or FLAIR. All tests have been done on T1w images to compare the obtained results with other of the state of the art using this type of acquisition sequence.

Concerning the medical images of *control subjects*, four different imaging sets. The first control structural MRI data were used from a group of 40 control subjects of the LPBA40 atlas. LPBA40 is composed of 20 males and 20 females; the average age at the time of acquisition was 29.20 years, within the 19-40 age group; 56 structures were manually labeled according to custom protocols using BrainSuite software (Shattuck et al. 2008a).

The second control structural MRI data were used from a group of 10 control subjects of the MGH10 atlas (Klein et al. 2009). MGH10 is composed of 4 males and 6 females; the average age at the time of acquisition was 25.3 years, within the 22-29 age group; 74 structures were manually labeled using Ghosh's ASAP software (Nieto-Castanon et al. 2003, Tourville, Guenther 2010).

The third control structural MRI data were used from a group of 18 control subjects of the IBSR18 dataset (Klein et al. 2009). This dataset is composed of 14 males and 4 females; the average age at the time of acquisition is 38.4 ± 4 years; 84 structures were manually labeled by the CMA (Center for Morphometric Analysis, Massachusetts General Hospital (MGH)).

The last control structural MRI data were used from a group of 12 control subjects of the atlas CUMC12 (Klein et al. 2009). These subjects were scanned at the Columbia University Medical Center on a 1.5 T GE scanner; 128 structures were manually labeled by one technician trained according to the Cardviews (Caviness et al. 1996) labeling scheme created at the CMA and implemented in Cardviews software (<http://www.cma.mgh.harvard.edu>).

Patient structural T1w MRI data were used from a group of 14 brain-damage patients. It was composed of 8 males and 6 females, average age was 40.83 ± 12.87 years. These patients were treated at the Guttmann Institut (Institut Guttmann - Neurorehabilitation Hospital 2014) on a 1.5T Toshiba scanner and on a 1.5T Siemens scanner.

IV.1.3. Brain atlases

Two different brain atlases have been used in this PhD both in the *pre-processing*, *registration* and in the *lesion identification* stages, as it will be explained later. Firstly, the atlas

MNI152 (Fonov et al. 2009) has been used mainly during the *pre-processing* stage. The methodological details to achieve this atlas can be found in (Fonov et al. 2011). Briefly described, images are pre-processed and intensity normalized to a range of 0-100. All T1w MRI data was then transform into the MNI stereotactic space using *minctracc* (Collins et al. 1994).

In order to identify anatomical structures with high probability to have been injured, the LPBA40 atlas (Shattuck et al. 2008a). This atlas is a series of maps of brain anatomic regions. These maps were produced from a set of whole-head MRI of 40 human volunteers. Each MRI was manually delineated to identify a set of 56 structures in the brain, most of which are within the cortex. These delineations were then transformed into a common atlas space to produce a set of co-registered anatomical labels.

IV.1.4. Development Tools

All the original algorithms implemented in this research work and presented in this document have been implemented by using the multi-paradigm numerical computing environment named MATLAB (Mathworks, Natick, MA, USA). The state of the art algorithms used at the evaluation stage are also implemented using this environment.

IV.2. Methods

IV.2.1. Proposed methodology

As mentioned in Section I, TBI and stroke will become the leading cause of disability and will be two of the health challenges with the greatest economic impact on health policies by 2030 according to WHO. Therefore, brain research is one of the most important challenges of this century as there is a great need to design and develop new technologies to improve brain knowledge.

Neuroimaging techniques may represent an important tool in rehabilitation after brain injury, since it may help in the prediction of long term outcomes and in the deeper understanding of brain mechanisms involved. Brain research is one of the main breakthroughs of European and American research programs in this century, as it has been mentioned in Section III.

Currently, most research studies are focused on extracting information only about the pathology of a certain functional area. On top of that, current rehabilitation treatments are planned according to the results of neuropsychological assessment batteries evaluating the functional impairment of each cognitive function and medical imaging information is not taken into account. However, on the one hand, recent research studies state that future neurorehabilitation therapies will probably consider the totality of pathology identified, rather than focusing on a particular area; on the other hand, the improvement in the efficiency of the neurorehabilitation treatments may be reached by making a design based on clinical evidence and personalization.

Therefore, it is necessary to design and develop new algorithms to automatically extract relevant information that can be used both for personalizing and evaluating neurorehabilitation treatments by using global and objective markers and for designing new data management strategies to classify and store medical imaging studies. In the last five years, there have been an increasing interest in developing these new algorithms by many research groups.

Regarding the automatic extraction of relevant information from neuroimaging studies, this PhD focuses on the extraction of information related to injured anatomical brain structures associated to stroke or TBI. As explained in Section I, the classical approach to identify lesions is to manually delineate brain anatomical regions. This approach presents several problems related to inconsistencies across different clinicians, repeatability and time. It is therefore desirable to automate this detection. Automated delineation of anatomical structures is done by registering brains to one another or to a template. However, brain pathological changes are always associated with intensity abnormalities and/or location alterations what makes traditional algorithms fail, requiring manually interaction by specialist to select landmarks or identify ROIs. Thus, both manual delineation and traditional registration algorithms present similar inconvenient.

This PhD proposes a methodology to automatically identify brain lesions made up of four main stages: pre-processing; singular points identification; registration and lesion detection, as shown in Fig.IV.1.

Figure IV. 1 Proposed automated lesion identification methodology.

These stages, in turn, are divided into different steps which are described in detail in the following sections. Figure IV.2 shows the workflow of each stage.

Figure IV. 2 Workflow of each stage of the proposed methodology

IV.2.2. Pre-processing

IV.2.2.1 Introduction

The pre-processing stage involves two types of normalization: intensity and spatial one. Previously, brain is isolated from extra-cranial or ‘non-brain’ tissues. This process is commonly known as skull-stripping. It has a direct impact on the quality of the normalization stage and subsequently, on the accuracy of the lesion identification stage (Smith 2002b). Figure IV.3 shows the pre-processing workflow used in this research work.

Figure IV. 3. Pre-processing pipeline used in this PhD.

Section III reviews the state of the art in skull-stripping, intensity normalization and spatial normalization. The main general conclusion states that although to establish a common intensity and spatial reference is crucial to obtain high quality data, neither a protocol nor which algorithms to use have generally been determined. These are the main detected problems that should be overcome:

- *On general.* There is a high variability among the acquisition parameters of MRI studies. This is reflected in studies with high differences regarding the number of slices, the different intensity values or even the orientation of slices. Therefore, it is important to use or develop algorithms to homogenize brain MRI studies regarding the dimensions of the volume ($m \times n \times p$, where $m \times n$ are the dimensions of each slice and p is the number of slices)
- *On the skull-stripping.* The high variability among subjects regarding both size and shape and among intensity information associated to the difference MRI devices, makes it difficult to differentiate between extra-cranial and brain tissues. In Section III, the state of the art in skull-stripping algorithms is reviewed, although there are several algorithms, none of them works properly for different studies, especially when the imaging studies belong to brain injury patients.
- *On the intensity normalization.* As previously mentioned, it is necessary to establish a common intensity reference to delimit the intensity variation window and obtain consistent results. As shown in the state of the art, there are several options that could be used. However, they all present some kind of inconveniences.
- *On the spatial normalization.* It is necessary to establish a common stereotactic reference. This type of normalization is crucial to obtain coherent results, as on the following stages, spatial information is the base of the lesion analysis. In this case, the state of the art of spatial normalization algorithm is reviewed in the ‘*Registration*’ subsection in Section III.

In the next paragraphs, the detected problems in each pre-processing stage are analyzed and the adopted solutions in this PhD are deeply described. It should be highlighted that although small contributions are proposed in this pre-processing stage, it is not the core of this research work.

IV.2.2.2 Skull-stripping

As previously mentioned, Table III. 2 in Section III summarizes the state of the art in skull-stripping algorithms. Almost all the reviewed algorithms are based on intensity and morphological characteristics of the imaging studies. These two types of characteristics are the most relevant when comparing “brain area” with “non-brain area”, as they permit to distinguish between them.

The large variability among intensity values of different medical imaging studies makes reviewed algorithms not to work properly in all cases. A fact that accentuates even more this intensity variability is that when a brain injury occurs, intensity values are often affected. Therefore, it is necessary to implement new robust and stable solutions against intensity variability. In this research work, we have designed and implemented two different approaches: an automatic approach based on tissue segmentation algorithms and a semi-automatic approach based on histogram analysis, morphology operations and region growing. Both algorithm are designed to be applied on one slice (two-dimensional) or on the whole volume (three-dimensional).

A. Automatic approach

The automatic approach is divided into three main stages, as shown in Fig. IV. 4. The first stage computes a mask for each type of tissue inside the ‘brain region’. In other words, it generates three different masks, one per each brain tissue: white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF). These masks are combined and normalized using a minimum value of zero and a maximum value of one [0, 1]. Finally, these masks are directly applied to the original image volume obtaining the original one without the skull.

Figure IV. 4 Workflow of the skull-stripping automatic approach.

The workflow used to obtain the tissue masks is based on a tissue probability segmentation algorithm and tissue probability maps. These probability maps are composed of imaging studies where prior probabilities of the voxels belonging to GM, WM and CSF are specified in the range of zero to one, they have been obtained from 152 young healthy subjects and they are provided by the Montreal Neurological Institute (MNI) (Evans et al. 1994). Fig.IV.5 shows the appearance these maps have.

Figure IV. 5 Tissue probability maps: GM, WM: CSF (Evans et al. 1994)

The segmentation algorithm is an expectation maximization (EM) approach widely used on SPM (Wellcome Trust Centre for Neuroimaging 2015). EM approach (Ashburner, Friston 2003) gives an efficient way for maximum likelihood estimation by alternating between an E-step, that estimates a priori tissue belonging probabilities based on a prior image, and a M-step, that computes the cluster of each tissue and the non-uniformity correction parameters.

These three masks are combined to define the binary mask that represents the ‘brain tissue’. In order to ensure that the intensity range of this mask varies from 0 to 1, ‘brain tissue’ mask is normalized according to Eq. IV.1.

$$I_{normalized} = \frac{I_{original} - \min(I_{original})}{\max(I_{original}) - \min(I_{original})} \quad (\text{Eq. IV.1})$$

Fig IV.6 shows an example of an original and a skull-stripped volume. As it can be observed, the automatic algorithm removes practically the totality of the scalp and meninges (‘non brain tissue’). The results are described in detail in Section V.

Figure IV. 6 Example of an automatic skull-stripping result. In the first row the original MR volume is displayed, whereas the second one shows the skull-stripped volume. This figure has been created with 3D Slicer (<http://www.slicer.org/>)

B. Semi-automatic approach

The semi-automatic approach is an iterative process divided into four stages: histogram analysis, morphology operations, region growing and binary normalization, as shown in Fig.IV.7.

Figure IV. 7 Workflow of the skull-stripping semi-automatic approach.

The first stage analyzes the histogram to extract a prior mask based on the intensity distribution. As shown in Fig.IV.8, ideally the intensity information of the image permits to distinguish each type of tissue.

Figure IV. 8 MRI T1w theoretical histogram. CSF: Cerebrospinal Fluid; WM: white matter; GM: gray matter.

However, the intensity values of the scalp and GM are very similar, which could lead to misclassification. In this step, the more frequent intensity corresponding to the background is identified and removed. Then, the mean intensity value of the rest of the histogram is computed and those intensity values which are below the mean are also removed. To ensure that none of the pixels of the original image contained inside the mask will be modified, all the holes inside the mask are filled and a closing morphology operation is performed. After, the user visually evaluates if the mask eliminates the corresponding areas to meninges and scalp or not.

In case that the mask needs to be refined, a volumetric region growing algorithm based on (Berglund et al. 2010) is applied until the mask covers only 'brain tissues' or eliminates as many scalp regions without removing 'brain tissue' as possible. Finally, as in the automatic approach, the intensity range of this mask is forced to vary from 0 to 1 (Eq.IV.1).

Fig. IV.9 shows an example of the semiautomatic segmentation algorithm. In this example only one iteration has been needed to obtain a mask covering 'brain tissue'.

Figure IV. 9 Example of a semi-automatic skull-stripping result. In the first row the original MR volume is displayed, whereas the second one shows the skull-stripped volume. This figure has been created with 3D Slicer (<http://www.slicer.org/>)

IV.2.2.3 Intensity normalization

Intensity normalization adjusts the variation range of the histogram of each image to a common scale. As shown in Table III.3, these type of algorithms are divided into six main modalities: even-order histogram derivatives; histogram matching; region-specific; registration; density functions and hybrid approaches. Most of these algorithms are used to normalize certain brain regions and the quality of the results depends on initialization parameters.

In this research work, the normalization should be global and not only applied on a certain brain region. As it will be used on patient images, where the intensity variability is still higher than in control subjects, the algorithm should not depend on initialization parameters. For both of these reasons, the algorithm used on this work is based on an histogram matching algorithm similar to (Weisenfeld, Warfteld 2004a) and on a range intensity adjust of the histogram, as shown in Fig.IV.10.

Figure IV. 10 Workflow of the intensity normalization

The histogram matching algorithm adjusts the ‘volume’ histogram to the ‘atlas’ one. First, it computes both histograms. Then, the cumulative distribution functions of both histograms are computed. The goal of this algorithm is to find for each gray level of the cumulative distribution of the ‘volume’ which gray level of the cumulative distribution of the ‘atlas’ is similar. Fig. IV.11 shows an example of how the histogram matching algorithm works. The Matched-histogram

volume presents a similar distribution to the atlas one, this means that the difference between GM and WM is enhanced. Finally, the intensity range of the algorithm is adjusted between [0, 1] (Eq.IV.1).

Figure IV. 11 Example of histogram matching algorithm.

IV.2.2.4 Spatial normalization

This stage is divided into two steps: dimension normalization and a 'rigid structure' normalization, as shown in Fig.IV.12. In the first step, the z dimension of the volume (see Fig.IV.13) is normalized, so every imaging volume, from this point on, have the same number of slices. In the second stage, a common stereotactic space for both images: the source image (volume) and the target image (atlas) is established.

Figure IV. 12 Workflow of the spatial normalization

Figure IV. 13 Brain system of coordinates. (Based on 3DSlicer presentation <https://www.slicer.org>)

As shown in Fig.IV.12, it is necessary to use an atlas on both steps. Table III.4 in Section III reviews brain adult atlases. In particular, the atlas used throughout this research work to normalize the dimension of volumes is the LPBA40 (Shattuck et al. 2008b), whereas to spatially normalize all the imaging studies the atlas used is the MNI152 (Mazziotta et al. 1995, Mazziotta et al. 2001a, Mazziotta et al. 2001b). This is due to the fact that the LPBA40 is the atlas used to identify the injured anatomical structures at the last stage (lesion detection, see Fig.IV.1). The main feature of this atlas is that it has 56 labeled structures, so it is important to maintain the dimensions of this atlas in order to ensure the quality of the lesion detection.

In order to normalize the dimension of the imaging studies used in this research work, we consider that all slices of the imaging volumes are completely perpendicular to the Z axis (see Fig.IV.13), although most slices of the imaging volumes are slightly inclined relative to the Z axis.

The dimension normalization is performed using a *reslice* algorithm based on a SPM (Wellcome Trust Centre for Neuroimaging 2015) function with the same name. This function modifies the volume dimension by interpolating the slices that are closer to the plane perpendicular to the Z axis if the volume to be normalized has less slices than the atlas; and eliminates the slices that are furthest to the perpendicular plane in the other case. The common case in this research work is the first one. In order to minimally modify the original imaging study, the nearest neighbor interpolation is used.

Once, imaging studies have the same dimensions, they are registered to spatially normalize the imaging studies. At this point, the use of two different types of registration algorithms was considered: a linear registration algorithm and a point set registration algorithm.

A. Linear registration algorithm

The linear registration is based on an affine algorithm similar to FLIRT (Jenkinson, Smith 2001)(Stockman, Shapiro 2001). Fig.IV.14 shows a common registration workflow composed of metric, optimizer and a transformation type. The metric defines the similarity between the source and the reference images to evaluate the accuracy of the registration. The optimizer determines the methodology to minimize or maximize the metric. The type of transformation defines how the source image may change to be aligned with the reference one. In particular, the transformation applied is affine, the interpolation is the nearest neighbor, the metric is the mattes mutual information and the optimizer is the '*One plus one evolutionary*' based on the gradient descent.

As shown in Fig.IV.14, initially, a transformation matrix is defined. The type of transformation combined with this matrix determines the transformation applied to the source image. This transformation is evaluated by computing the similarity between source and target images, the way of measuring this similarity is specified through the metric. The optimizer proposes a new matrix to improve the obtained results. This iterative process will finish when either configure metric value or maximum number of iterations is reached. At this point, the source image is modified according to the transformation matrix by using an interpolation method. Regarding the type of optimizer, the ones based on gradient descent adjust the processing parameters to minimize changes on gradient. An 'evolutionary algorithm iterates until finding a set of parameters producing the best results by changing these parameters on the

last iteration (the parents). If the new parameters (children) produce a better result, then the children become new parents, thus, these parameters are modified again. If the parents produce a better result, this set of parameters remains as parents and the process finishes.

Figure IV. 14 Workflow of the linear registration algorithms.

B. Point set registration algorithm

The point set registration algorithm consists on finding a spatial transformation that aligns two point sets. Point sets are obtained with detector algorithms. Although, these algorithms are explained in detail on the next stage ('singular point identification'), they are briefly introduced in this section as they are necessary to identify the points that will be used to find the spatial transformation. The detector used in this stage is the canny edge detector (Canny 1986) described in Section III. As the goal of the registration at the pre-processing stage is to align rigid structures as a first approach to compute the transformation that puts into spatial correspondence both imaging studies, the detector may detect points located particularly on contours. Consequently, the canny detector is an appropriate detector. Fig.IV.15 shows a general workflow of a point set registration algorithm.

Figure IV. 15 Workflow of the point set registration algorithm.

This research work compares two different point set registration algorithm with the linear registration algorithm explained above. In particular, the algorithms that are compared are the ‘iterative closest point’ (ICP) (Bergström, Edlund 2014) and the ‘Coherent point drift’ (CPD) (Myronenko, Song 2010). Results are shown in Section V.

ICP iteratively computes the transformation needed to minimize the distance between the source and the reference point set. Firstly, it estimates the transformation using re-weighted least squares. Then, source point set is transformed according to this transformation matrix. This process finishes when the distance between the source and target data sets reach a minimum distance.

CPD considers the alignment between two different point sets as a probability density estimation problem. The source point set is modelled as centroids of a Gaussian mixture model (GMM). This set is forced to fit the reference point set by maximizing the likelihood. These GMM centroids are moved coherently as a group to preserve the topological structure of the point set. GMM centroid locations are recalculated with rigid parameters and derived a closed form solution of the maximization step of the EM algorithm in arbitrary dimensions.

In order to minimize the changes within the patient/control subject imaging study, in this research work, the atlas is modified to be in spatial correspondence with the patient/control subject imaging study. In other works, the source image is the atlas and the reference image is the patient/control subject one.

IV.2.2.5 Conclusions

This section describes the algorithms used at the pre-processing stage. This stage is fundamental to prepare the data to be processed and analyzed at the following stages. In particular, the pre-processing stage is divided into three main steps: skull-stripping, intensity normalization and spatial normalization.

In the first step, the scalp is eliminated from images because registration robustness is improved if ‘non-brain parts’ are removed and in brain atrophy estimation, it helps to disambiguate brain tissue from other parts of the images such as CSF (Smith 2002b). In this PhD work two different approaches (automatic and semiautomatic) are compared by using both a control subject and a patient dataset. The automatic approach is based on the SPM to create GM, WM and CSF compartments. The sum of these compartments are binarized to obtain brain masks. The semiautomatic approach is based on histogram analysis and region growing.

The second stage adjusts the variation range of the histogram of each study to a common scale. This PhD uses an approach based on a histogram matching algorithm and a range intensity adjustment to intensity normalize imaging volumes.

Finally, the spatial normalization is divided into a dimension and a ‘rigid-structure’ normalization. In the first stage, imaging volumes are normalized regarding orientation and physical volume dimension. This stage is performed by using an algorithm based on the *reslice* algorithm of SPM. In the second stage, rigid structures are put into spatial correspondence. Three different approaches are compared: a linear registration algorithm and two different point set registration algorithms (ICP and CPD).

The results are explained in detailed and discussed in Section V.

IV.2.3. Singular points identification

IV.2.3.1 Introduction

The singular points identification stage involves three steps: (A) singular points location, (B) orientation assignment and (C) descriptor generation. Figure IV.3 shows the workflow used to identify and characterize singular points in this research work. The aim of the first stage is to identify those points whose imaging characteristics are different from their neighbors. Then, an orientation is assigned to each singular point based on local image properties. Finally, the spatial information is integrated with the imaging characteristics of each singular point neighborhood into a matrix structure named descriptor.

Figure IV. 16 Singular points identification pipeline used in this PhD.

Section III reviews the state of the art in singular points location, orientation assignment and imaging descriptors. Identification and characterization of imaging features play an important role in most of the image analysis and processing applications. In particular, in this PhD framework, the identification and characterization of imaging features allow to label anatomical regions and therefore to identify anatomical structures that may be injured.

The review of the state of the art, mentioned above, analyzes different algorithms that can be used on the key stages of a descriptor algorithm (shown in Fig.III.8). Firstly, different type of features and detectors are reviewed. In medical imaging, detectors are widely used in applications such as segmentation, shape and volumetric reconstruction, registration, lesion characterization and imaging retrieval. The most common features used in these applications are edges, corners and blobs. Although there are several medical applications based on detectors, we have hardly found direct applications in brain imaging.

Regarding the orientation assignment, we have reviewed six different approaches to compute the orientation assignment of each singular point regarding their neighborhood: intensity differences, gradient histogram, Haar wavelets, smoothed gradient, center of mass and histogram of intensities. The orientation assignment approach depends on the chosen descriptor algorithm.

Descriptor algorithms have been increasingly used in different medical imaging applications such as registration, segmentation, model generation, anatomical region detection and CBIR. SURF and SIFT are the most commonly used algorithms in these applications. However, medical imaging modalities, such as CT or MRI, involve non-linear intensity changes that directly affect the functioning of these algorithms as they are invariant to linear intensity changes (Sargent et al. 2009, Kelman, Sofka & Stewart 2007). Thus, these algorithms may be adapted to be used on a medical context. In the following paragraphs, the main detected problems that should be overcome are mentioned:

- *On general.* Descriptor algorithms combine intensity and location information to identify and characterize singular points on images. These algorithms are divided into three main stages that are deeply reviewed in Section III. The combination of different type of detectors together with the development of new algorithms adapted to the characteristics of medical imaging studies, in particular T1w-MRI, may improve the detection of singular points. This means that more information is analyzed to perform the registration, giving as a result those anatomical structures that differ from the normal ones, as it is explained in detail below.
- *On the singular point location.* Singular points, also known as features, are grouped into four main types: edges, corners, blobs and ridges. This classification is based on the eigenvectors and eigenvalues obtained from the second order matrix of the intensity values. The most common features are the three first ones.
- *On the orientation assignment.* It characterizes each singular point regarding the intensity variation of their neighbors. The six main types of orientation assignment computation and the selected approach depend on the descriptor algorithm.
- *On the imaging descriptor.* The descriptors commonly used on medical applications are SIFT and SURF. The characteristics of medical imaging studies, such as MRI and CT, make it necessary to adjust these algorithms in terms of the identification of intensity variation.

In the next paragraphs two different descriptor algorithms are proposed. The first one is based on SURF algorithm but it introduces important changes that improves the identification of singular points. This algorithm is named ‘Brain Feature Descriptor’ (BFD) and it is one of the contributions of this PhD. This descriptor works slice by slice, in other words, is a two-dimensional approach. The second one is the volumetric extension of the BFD algorithm. This approach works over the whole imaging volume and it is the second contribution of this PhD in terms of descriptor algorithms.

IV.2.3.2 Two-dimensional blob descriptor algorithm: Brain Feature Descriptor (BFD)

As previously mentioned, main phases of a descriptor algorithm are: location of points of interest, orientation assignment and descriptor generation, as shown in Fig.IV.16. At the first stage, the aim is to detect points featuring special characteristics, blobs in this proposed descriptor. Although as it will be explained later, the final solution is defined, in this work, as a multi-detector one, as it involves three different types of image features. Filters used to find these characteristics are structured in a pyramidal way, known as scale-space, also explained later. At the orientation assignment stage, maximum gradient direction of each landmark is obtained. Finally, information relative to location, orientation and gradient values is stored in a matrix structure, named descriptor.

The proposed descriptor algorithm is based on SURF algorithm (Bay et al. 2008). SURF and BFD algorithms take as input the cumulative distribution of image intensity values, also known as integral image (Viola, Jones 2001). This imaging representation is directly related to the decrease of processing time in relation to similar descriptor algorithms, such as SIFT. The integral image at location (x, y) contains the sum of the pixels above and to the left of this location, inclusive, as in Eq.IV.1.

$$Int_{Image} = \sum_{x' \leq x, y' \leq y} Image(x', y') \quad (Eq.IV.1)$$

As shown in Fig.IV.17-A, the sum of the pixels within the blue rectangle are computed with four array references (A, B, C and D). Fig.IV.17-B shows the computation of the integral image on a real brain MRI-wT1. This type of image representation permits to obtain the cumulative intensity distribution function of an image. This function is crucial to identify blob features by optimizing computational cost.

Figure IV.17 Integral Image. A-Theoretical approach of the integral image computation. B-Integral image computation of the brain MRI.

Detector filters used to find singular points are structured in a pyramidal way, known as scale-space. Scale-space approach is a multi-scale representation of a signal or image in an ordered set of derived signals or images intended to represent the original signal at different levels of scale (Lindeberg 2013). One of the main arguments behind this type of imaging representation is that, if no prior information is available about what are the appropriate scales for a given data set, then the only reasonable approach for an uncommitted vision system is to represent the input data at multiple scales. This means that the original signal should be embedded into a one-parameter family of derived signals, in which fine structures are successively suppressed. This parameter is commonly named σ .

Fig IV.18 shows a general scheme of the scale-space concept, as shown, the bigger the σ is, the coarser the structures detected (Fig IV.18.A). Fig IV.18.B shows the scale-space approach used in this PhD work. There are two possibilities to generate the scale-space: either image or filter multi-scale representation. As shown in the following figure, both SURF (Bay et al. 2008) and BFD generate the scale-space of filter, in particular a filter that represents the approximation of the Hessian-based detectors, explained below.

Figure IV. 18 Scale-space approach. A: General scheme of a scale approach approximation. B: SURF and BFD Scale-space set-up. [Based on: (Bay et al. 2008)]

In particular, the scale space is divided into octaves. A filter with increasing size is convolved with the same input image obtaining a series of filter response maps in each octave. The change of octave implies an increase in the filter size and in the sampling frequency of 2^{octave} . An octave, in turn, is subdivided into a constant number of scale levels. The filter size (FS) depends on the octave (OCT) and the scale level (SCL), as in Eq.IV.2.

$$FS = 3 * (2^{\text{OCT}} * SCL + 1) \quad (\text{Eq.IV.2})$$

Fig.IV.19 shows the scale space configuration. It starts with the 9x9 filter which computes the response map for the smallest scale. This figure shows inside each box the lobe size (LS) – filter size (FS), being the filter size three times the size of the lobe, as it is explained later. Octaves are overlapping in order to cover all possible similar scales.

	SCL 1	SCL 2	SCL 3	SCL 4
OCT 4	17-51	33-99	49-147	65-195
OCT 3	9-27	17-51	25-75	33-99
OCT 2	5-15	9-27	13-39	17-51
OCT 1	3-9	5-15	7-21	9-27

Figure IV. 19 Scale-Space configuration: (lobe size – filter size)

There are interesting relations between scale-space approach and the biological vision, since the mammalian retina and visual cortex can be modelled by a non-isotropic affine scale-space model, a spatio-temporal scale-space model and/or non-linear combinations of such linear operators (Lindeberg 2011).

The following paragraphs describe the descriptor proposed in this PhD work, named ‘Brain Feature Descriptor’ (BFD), and the similarities and differences compared with the SURF descriptor algorithm.

Location of points of interest

As shown in Section III, there are many algorithms aiming to detect blob features such as Laplacian of Gaussian (Ryan, McNicholas & J Eustace 2004) or the Hessian-Laplace detector

(Torsten Bert Moeller, Emil Reif 2007). As in original SURF, in BFD, the determinant of the Hessian matrix (Lindeberg 1998) is used to detect blob features. Given a certain point inside the image $P = (x, y)$, the Hessian matrix $H(P, \sigma)$ in P at a scale σ is defined as in Eq.IV.3.

$$H(P, \sigma) = \begin{bmatrix} L_{xx}(P, \sigma) & L_{xy}(P, \sigma) \\ L_{xy}(P, \sigma) & L_{yy}(P, \sigma) \end{bmatrix} \quad (\text{Eq.IV.3})$$

Where $L_{xx}(P, \sigma)$, $L_{yy}(P, \sigma)$ and $L_{xy}(P, \sigma)$ are the convolution of the Gaussian second derivative with the image in point P , also known as Laplacian of Gaussian (LoG), as in Eq. IV. 4.

$$L_{xx} = \frac{\delta^2}{\delta x^2} g(P, \sigma) = -\frac{1}{\pi\sigma^4} \left[1 - \frac{x^2+y^2}{2\sigma^2} \right] e^{-\frac{x^2+y^2}{2\sigma^2}} \quad (\text{Eq.IV.4})$$

Theoretically, Hessian matrix is estimated by calculating the LoG. However, as real filters are non-ideal in any case, the Hessian matrix is approximated with the Lowe's approximation of LoG (Lowe 1999a). Fig.IV.20 shows the 3D representation (A) and the top view (B) of the $L_{xx}(P, \sigma)$ and $L_{xy}(P, \sigma)$, respectively. Fig.IV.20.C shows $D_{xx}(P, \sigma)$ and $D_{xy}(P, \sigma)$, the approximation of the $L_{xx}(P, \sigma)$ and $L_{xy}(P, \sigma)$ with box filters. Both SURF and BFD use the approximation based on box filter to compute the Hessian matrix.

Figure IV. 20 Laplacian of Gaussian filters. A- 3D representation. B- Top view of the 3D representation. C- Approximation of the LoG filters with box filters. ($\sigma = 1$).

As previously mentioned, box filters have been used to approximate the Hessian matrix in the Cartesian coordinate x , y and xy direction. Filters are structured in the form of squared boxes. Where LS represents the size of the filter's lobe and FS is the size of the filter. Therefore, the size of the filter will be three times the size of the lobe, as shown in Fig.IV.21. The filter of the figure (9x9 box) represent the lowest scale, in other words, the highest spatial resolution.

Figure IV. 21 Box filter dimensions: LS: lobe size; FS: filter size.

SURF computes the determinant of the Hessian by using the approximation of the Laplacian as in Eq.IV.5. The weight (w) is the energy conservation between the LoG kernels and the approximated LoG kernel as in Eq.IV.6, where $|x|_F$ is the Frobenius norm, $\sigma = 1.2$ and $FS = 9$. This energy is considered a constant regardless of the size of the filter (FS).

$$\det(H) = D_{xx}D_{yy} - (wD_{xy})^2 \quad (\text{Eq.IV.5})$$

$$w = \frac{|L_{xy}(P,\sigma)|_F |D_{yy}(FS)|_F}{|L_{yy}(P,\sigma)|_F |D_{xy}(FS)|_F} \cong 0.9 \quad (\text{Eq.IV.6})$$

This energy is considered a constant regardless of the size of the filter (FS). However, as shown in Fig IV.21, it varies according to the filter size. This energy value has a direct impact on the detection of blobs, since the determinant of the Hessian determines which imaging points correspond to this type of features. This impact is analyzed below.

Figure IV. 22 Variation of w depending on the filter size.

For the purposes of adjusting the w value to the size of the filter, we have proposed an analytical approach, shown in Fig.IV.23 and Eq.IV.7, where FS is the size of the filter. The proposed approach is based on the size of the filters of the two first octaves, as it is in these two octaves where the coarser imaging details, in our case anatomical structures, are detected. R^2 indicates the similarity between the analytical approximation and the real variation of w .

Figure IV. 23 Analytical approach of the energy parameter (w). R^2 indicates the similarity between the real variation and the approximation, the closer to the unit value, the more similar.

$$w = \frac{1}{\sqrt{2}} + \frac{99}{2500}FS - \frac{23}{10000}FS^2 + 6 \cdot 10^{-5}FS^3 - 5 \cdot 10^{-7}FS^4 \quad (\text{Eq.IV.7})$$

The original SURF does not take into account local contrast variations as it is designed for the application in computer vision applications where the images used to be RGB images. Thus, there are enough information to detect blob features. However, in order to ensure the identification of these type of features in intensity images, such as medical imaging studies, filters must be independent from local contrast changes. In particular, the proposed filters are normalized with respect to the standard deviation (SD) of pixel values affected by them as in Eq.IV.8, where F is the filter used to detect blobs, FS is the size of the filter, SD is standard deviation and D_{ij} is one of the three box filters (D_{xx} , D_{yy} and D_{xy}) used to obtain the Hessian matrix. If SD is zero, imaging points presenting very low contrast value are not considered as detected landmarks.

$$F(x, y, FS) = \begin{cases} \forall SD(x, y, FS) > 0, & \frac{H_{ij}(x, y, FS)}{SD(x, y, FS)} \\ \forall SD(x, y, FS) = 0, & 0 \end{cases} \quad (\text{Eq.IV.8})$$

Therefore, BFD takes into account only intensity values of pixels affected by each filter and it makes intensity dispersion independent regarding contrast. In order to calculate standard deviation (I_{SD}) in a fast way, an integral square representation of the image is used. It is obtained by using the same equation to calculate the integral image (Eq.IV.9), where A , B , C and D are the vertex of a rectangle, similar to Fig.IV.17.

$$I_{SD} = A + D - (C + B) \quad (\text{Eq.IV.9})$$

Regarding the impact of the changes on the calculation of w and the normalization mentioned in the preceding paragraph, Fig.IV.24 shows the differences between SURF and BFD. The main difference is the regions where the points are identified. These differences are deeply analyzed in Section V.

Figure IV. 24 SURF vs BFD. Differences between both types of algorithms. The center of each circle represents the detected singular point and the radius of each circle represents the scale where each one is detected.

The scale-space is analyzed by up-scaling the size of the filters. Both SURF and BFD identify blob features by computing the maximum and minimum of the determinant of the Hessian matrix. In particular, to find a set of candidate points, each point is compared to its 26 neighbors: 8 in the native scale and 9 in the above and below scales (shown in Fig.IV.25). The red pixel in the Fig.IV.24 is selected as maxima if it is greater than the surrounding pixels on its scale and the above and below scales.

Figure IV. 25 Maximum and minimum computation. Based on (Bay et al. 2008)

To find the spatial location of the set of candidates point, taking into account also the scale where the point is found, the determinant of the Hessian is expressed as a Taylor expansion where the quadratic terms are centered at the detected location (Bay et al. 2008, Brown, Lowe 2002), as in Eq.IV.10. The interpolated location $P_i(x, y, \sigma)$ is found by obtaining and setting to zero the derivative function of the Taylor expansion (Eq.IV.11). If P_i is greater than 0.5 in the x , y or σ directions, the location is adjusted and the interpolation is repeated until $P_i < 0.5$. Those points that do not converge to this value, are removed as they not repeatable and stable.

$$H(x) = H + \frac{\partial H^T}{\partial x} x + \frac{1}{2} x^T \frac{\partial^2 H}{\partial x^2} x \quad (\text{Eq.IV.10})$$

$$P_i = -\frac{\partial^2 H^{-1}}{\partial x^2} \frac{\partial H}{\partial x} \quad (\text{Eq.IV.11})$$

Orientation assignment

The orientation of a descriptor describes the intensity distribution of each singular point neighborhood. Fast-Hessian is used to compute this distribution as in (Lowe 2004a, Bay et al. 2008). Haar wavelets, shown in Fig.IV.26, permit to find gradients in the x and y directions and they are efficient regarding the computation time. The size of the Haar wavelets used to determine the orientation is 4σ . These wavelets are applied on a set of pixels within a radius of 6σ of the detected point. Where σ is, in both cases, the scale where the point is identified.

Figure IV. 26 Haar wavelets

Wavelet responses are weighted with a Gaussian centered at the detected point. The Gaussian has a standard deviation of 2.5σ . The dominant orientation is estimated by calculating the sum of all responses within a sliding window of size $\pi/3$, as shown in Fig.IV.27. The longest vector corresponds to the orientation of the point.

Figure IV. 27 Orientation assignment

Descriptor generation

To generate the descriptor, a square region is centered on each detected landmark. These squared regions are split up into smaller 4×4 square sub-regions. On each sub-region approximate Haar wavelets are computed at 5×5 spaced sample points, as shown in Fig.IV.28.

Figure IV. 28 Descriptor generation

In contrast to the Haar wavelets used to determine the orientation, the size of these wavelets is 2σ , where σ continues to be the scale where the point is detected. For each sub-region the gradient in x , in y and the modules of each intensity variation is computed. To sum up, each detected singular point is composed of 4 sub-regions that contribute with 4 values each one. Therefore, each descriptor row has a length of 64 in SURF. BFD contains: spatial information ((x) x -coordinate, (y) y -coordinate, (σ) size of the filter, (L) value of the Laplacian, (Sen) sinus of the orientation, (Cos) cosines of the orientation and the 64 length vector with the intensity-related information (H_x , $|H_x|$, H_y and $|H_y|$). These two last stages are common to SURF and BFD.

IV.2.3.3 3D-Blob descriptor algorithm: 3D-BFD

The extension of BFD to 3D is also proposed in this PhD work. Even if it may look like a direct change in the beginning, it is necessary to introduce changes and new concepts that are described in the following paragraphs. In literature (Section III), not many research works describing 3D descriptors have been found, since this type of algorithms have been broadly applied on computer vision applications where images are two-dimensional. However, there is a growing interest towards using descriptors on medical image applications. Most of these algorithms are extensions of SIFT (Feulner et al. 2011, Flitton, Breckon & Bouallagu 2010, Ni et al. 2009a) and they are commonly used to annotate images in 'Content based image retrieval' (CBIR) systems but not with the pursued objective of this PhD.

This algorithm, named '3D Brain Feature Descriptor' (3D-BFD), also takes as input the cumulative distribution of image intensity values, known as integral image volume. In this case, the task of calculating the volume of a cubic is reduced to eight operations, considering a cubic bounded by vertices A , B , C , D , E , F , G and H . The sum of intensities, shown in Fig.IV.29.I, is computed as in Eq.IV.12.

$$Int_{Volume} = \sum_{x' \leq x, y' \leq y, z' \leq z} Volume(x', y', z') \quad (\text{Eq.IV.12})$$

The original volume (right Fig.IV.29.II) is compared to the integral volume (left Fig.IV.29.II), the integral volume at location (x , y , z) contains the sum of the pixels above and to the left of

this location, inclusive, as well as in the integral image. Fig.IV.29.III shows an example of one slice (axial, sagittal and coronal view) of the integral volume vs the original image.

Figure IV. 29 Integral volume. I: Integral volume concept. II: Integral volume vs original volume. III: Example of one slice (axial, sagittal and coronal view) of the original vs integral volume.

The volume-scale-space concept, shown in Fig.IV.18.A, is similar to conventional scale-space concept. This means that the volume-scale-space represents the way in which filters are designed, following a multi-scale representation where σ indicates the detail level detected by the filters. In other words, the bigger the σ , the coarser the structures detected.

The design and configuration of the volume-scale-space is similar to the scale-space, it is also divided into octaves. Each octave is subdivided into a constant number of scale levels and according to the number of scale levels, a series of response maps are obtained in each octave. The bigger the octave, the bigger the filters. The size of the filters are computed as in Eq.IV.2. The volume-scale-space configuration, as in Fig.IV.19, starts with the 9x9x9 filter which corresponds to the smallest scale.

Location of points of interest

The determinant of the Hessian matrix is used to detect blob features as in Eq.IV.13, where $P = (x, y, z)$, $H(P, \sigma)$, σ is the scale and $L_{xx}(P, \sigma)$, $L_{yy}(P, \sigma)$, $L_{zz}(P, \sigma)$, $L_{xy}(P, \sigma)$, $L_{yz}(P, \sigma)$, $L_{zx}(P, \sigma)$ are the LoG, as in Eq.IV.14.

$$H(P, \sigma) = \begin{bmatrix} L_{xx}(P, \sigma) & L_{xy}(P, \sigma) & L_{xz}(P, \sigma) \\ L_{xy}(P, \sigma) & L_{yy}(P, \sigma) & L_{yz}(P, \sigma) \\ L_{xz}(P, \sigma) & L_{yz}(P, \sigma) & L_{zz}(P, \sigma) \end{bmatrix} \quad (\text{Eq.IV.13})$$

$$L_{xx} = \frac{\delta^2}{\delta x^2} g(P, \sigma) = -\frac{1}{\pi \sigma^4} \left[1 - \frac{x^2 + y^2 + z^2}{2\sigma^2} \right] e^{-\frac{x^2 + y^2 + z^2}{2\sigma^2}} \quad (\text{Eq.IV.14})$$

Hessian matrix is also approximated with box filters based on the Lowe's approximation of LoG (Lowe 1999a). Fig.IV.30-left shows the volumetric representation of $L_{yy}(P, \sigma)$, $L_{yz}(P, \sigma)$ and $L_{xy}(P, \sigma)$, whereas Fig.IV.30-right shows the box filters ($D_{yy}(P, \sigma)$, $D_{yz}(P, \sigma)$ and $D_{xy}(P, \sigma)$) used to approximate $L_{yy}(P, \sigma)$, $L_{yz}(P, \sigma)$ and $L_{xy}(P, \sigma)$, respectively.

Figure IV. 30 Laplacian of Gaussian filters. Right: 3D representation. Left: Box filters.

The determinant of the Hessian is computed as in Eq.IV.15, where w is the energy conservation between the LoG kernels. The analytical value of w obtained for BFD is assumed to

be equivalent in BFD-3D. Thus, it is calculated as in Eq.IV.16. This weight takes into account the different size of the filters (FS), and thus, it compensates the box filters approximation.

$$\det(H) = D_{xx}D_{yy}D_{zz} - w^2[D_{xx}D_{yz}^2 + D_{yy}D_{xz}^2 + D_{zz}D_{xy}^2] + 2w^3D_{xy}D_{yz}D_{xz} \quad (\text{Eq.IV.15})$$

$$w = \frac{1}{\sqrt{2}} + \frac{99}{2500}FS - \frac{23}{10000}FS^2 + 6 \cdot 10^{-5}FS^3 - 5 \cdot 10^{-7}FS^4 \quad (\text{Eq.IV.16})$$

In order to take into account local intensity values and enhance local contrast, filters are normalized by the intensity standard deviation, as in Eq.IV.17. Intensity standard deviation is computed as in Eq.IV.18, where N is the number of voxels affected by the filter. Hence it is the filter volume.

$$F(x, y, z, FS) = \begin{cases} \forall SD(x, y, z, FS) > 0, & \frac{H_{ij}(x, y, z, FS)}{SD} \\ \forall SD(x, y, z, FS) = 0, & 0 \end{cases} \quad (\text{Eq.IV.17})$$

$$SD = \sqrt{\frac{1}{N} \sum_{i=1}^N (i_i - \bar{i})^2} \quad (\text{Eq.IV.18})$$

The volume-scale-space is also analyzed by up-scaling the volume of the filters. Blob features are identified by computing the maximum and minimum of the determinant of the Hessian matrix. Each candidate point is compared to its 26 neighbors in the native scale and 27 in the above and below scales, shown in Fig.IV.31. If the red voxel is greater than the surrounding voxels on its scale and the above and below scales, it is selected as maxima.

Figure IV. 31 Volume-scale-space analysis.

Orientation assignment

The intensity distribution of the neighborhood of each singular point is computed by applying 3D Haar wavelets (Ahmad et al. 2009) (Fig.IV.32), permit to find gradients in x, y and z directions. The size of the Haar wavelets is 4 times the value of the scale where the point is identified. Haar responses are also weighted with a Gaussian whose standard deviation value is 2.5 times the scale where the point is identified and it is centered at the detected point.

Figure IV. 32 3D Haar Wavelets

The dominant orientation is estimated by calculating the sum of all responses within a spherical cap equivalent to the $\pi/3$ sliding window of BFD and SURF, whose radius has a value of 6σ , where σ is described in Eq.IV.19.

$$\sigma = 0.4 * (2^{octave} * scale_{level} + 1). \quad (\text{Eq.IV.19})$$

This spherical cap is divided into regular regions to estimate the sum of responses. In particular, vertex and the middle points to each edge of a rhombic triacontahedron are used to divide the space into spherical caps of around $\pi/6$, as shown in Fig.IV.33.

Figure IV. 33 Rhombic triacontahedron used to divide the space into regular regions to compute the orientation.

Descriptor generation

A cubic region is centered on each detected landmark, these regions are, in turn, divided into 4×4 cubic sub-regions. On each sub-region a Haar wavelet of size 2 times the scale where the point is detected, are computed at 5×5 spaced sample points, as shown in Fig.IV.34. For each region, the gradient in x, y and z and the corresponding modules of each intensity variation is computed. 3D-BFD descriptor contains: spatial information of each singular point (x-coordinate, y-coordinate, z-coordinate, value of the Laplacian) and a 94 length vector with the intensity-related information (H_x , $|H_x|$, H_y , $|H_y|$, H_z and $|H_z|$)

Figure IV. 34 3D Descriptor generation.

IV.2.3.4 Two-dimensional multi-detector descriptor approach

Brain anatomical structures are usually manually delineated by identifying sulcus, gyrus or lobules (an example is shown in Fig.IV.35. where a sulcus, gyrus and lobule are delineated). This delineation process consists mainly of detecting imaging features such as edges or corners. Therefore, the integration of these two types of features with blobs may improve the subsequent registration process to detect anatomical structures with high probability of being injured. Section V analyzes and quantifies this improvement.

Figure IV. 35 Brain anatomical structures manually delineated: cingulate sulcus, cingulate gyrus paracentral lobule. (Sagittal view) [Source: www.innerbody.com]

In particular, this PhD proposes to integrate Harris detector (Harris, Stephens 1988b) to detect corners and Prewitt operator (Prewitt 1970) to identify edges, both described in Section III, with BDF. These three types of imaging features permit to create a grid that, as it is explained in detail below, divides brain region into homogenous sub-regions, as they cover both cortical and subcortical areas (Fig.IV.36.B). Fig.IV.36.A shows an example of the spatial distribution of these three type of points within the brain region. Both Prewitt and Harris are located mostly on cortical areas, whereas BFD points also cover subcortical areas.

Figure IV. 36 A: Spatial distribution of different type of imaging features: Harris, Prewitt and BFD points. B: Cortical vs subcortical regions.

Each single-point specifies the center location of a neighborhood, which is described through feature vectors on each type of detected singular point: Harris, Prewitt and BFD, also named descriptors, as previously mentioned. Harris and Prewitt descriptors describe, like BFD descriptor, the intensity distribution of the neighborhood of each singular point, in such a way that singular points are completely characterized.

IV.2.3.5 Three-dimensional multi-detector descriptor approach

Just as the two-dimensional approach, three-dimensional approach also integrates different types of detectors. In particular, a 3D edge detector is integrated with the 3D BFD. In this case a 3D Canny detector (Bähnsch, Stelldinger & Köthe 2009) is used to detect edges based on the original detector (Canny 1986). In both cases, the neighborhood of each singular point is characterized through the intensity distribution or gradient distribution.

Fig.IV.37 shows an example of both type of descriptors, as in the two-dimensional approach, the singular points detected with both algorithms are complementary, since Canny detects most of the singular points around cortical areas and 3D BFD detects points also in subcortical regions.

Figure IV. 37 Volumetric distribution of singular points detected by 3D Canny (left) and 3D BFD (right)

IV.2.3.6 Conclusions

This section describes the algorithms used to detect and characterize singular points. This stage permits to automatically identify singular points, also named landmarks, which are the basis for the registration algorithm, described below. The identification of singular points is divided into three main stages: (A) singular point location, (B) orientation assignment and (C) descriptor generation.

This PhD proposes a two-dimensional blob descriptor algorithm, named BFD. This algorithm is based on the basis of the SURF algorithm and it proposes changes to adequate SURF filters to the characteristics of MRI images. Since most of the medical imaging studies are volumetric, this PhD also proposes the volumetric extension of BFD, named 3D BFD.

In order to improve the subsequent registration process, whose main objective is to detect anatomical structures with high probability of being injured, this PhD proposes the integration of other detectors. In the case of the two-dimensional approach, three different type of features: edges, corners and blobs described each MRI slice. Harris detector detects corners, Prewitt operator to identify edges and BFD to detect blobs, are integrated. Both Prewitt and Harris are located mostly on cortical areas, whereas BFD points also cover subcortical areas. In the case of 3D, this PhD proposes to integrate an edge detector, a 3D Canny detector, with the 3D BFD. 3D Canny detector identify points around cortical areas and BFD detects points also in subcortical regions. In both cases, the neighborhood of each singular point is characterized through the intensity gradient distribution.

The results are explained in detailed and discussed in Section V.

IV.2.4. Registration

IV.2.4.1 Introduction

As previously mentioned, automatically determining anatomical correspondence is almost universally done by registering brains to one another or to a template for studies in non-damaged brains (Klein et al. 2009)(Klein et al. 2009). However, in pathological conditions, handmade delineation of brain regions is the classical approach for establishing anatomical correspondence. This is an important methodological limitation as handmade labeling techniques suffers from inconsistencies within and across human labelers (Klein et al. 2009, Fiez, Damasio & Grabowski 2000, Towle et al. 2003) and are very time-consuming processes, hindering their extended use in clinical scenarios (Powell et al. 2008).

Several automated algorithms have been developed to automatically label brain structures, as reviewed in Section III. One of the major conclusions of the referenced papers in Section III, is that most of these algorithms might not be suitable in some cases such as anatomical lesions, which introduce topological differences varying in magnitude and are always associated with intensity abnormalities and/or location alterations (Rodriguez-Vila, Garcia-Vicente & Gomez 2012). These alterations are the cause that physical one-to-one correspondence between images may not exist due to the insertion or removal of some imaging content. This inconsistency between two image studies could severely reduce the performance of registration algorithms based on intensity imaging parameters. Consequently, in order to use these algorithms on structural MRI studies of patients with brain lesions, specialists may have to manually interact with the affected region on the scans or select manual landmarks to compute the spatial transformation between studies. Nevertheless, both possibilities have the same drawbacks of the manual delineation highlighted above.

Another conclusions having direct relation with the aforementioned conclusion is that there are barely registration algorithms used to identify anatomical structures affected by brain injury. In particular, most of the reviewed landmark-based registration algorithms use intensity as the main information to compute the geometrical transformation and assume that small deformations are sufficient to register set of images. However, lesions associated to some strokes and TBI can affect great and disperse areas.

The automation of the landmarks' selection process can be done using the combination of intensity and location information and may help develop algorithms to automatically identify changes associated with lesions (Wang et al. 2010). Therefore, descriptors may help in the automatic detection of landmarks, commonly referred to in this PhD as 'singular points'.

This PhD proposes a registration algorithm based on descriptors, named 'Brain Feature Registration Algorithm' (BFRA). This method, together with the multi-detector approach previously described, not only automatizes the manual marking of landmarks by specialists, releasing time resources, but also increments the number of selected landmarks, which means that the registration process takes into account more information.

Fig.IV.38 shows the overview of the proposed algorithm. BFRA is composed of three main stages: (A) matching among singular points, (B) the generation of a mesh based on the matched

singular points, and lastly, (C) the computation of the non-linear transformation based on the meshes.

Figure IV. 38 Registration pipeline proposed in this PhD

The next paragraphs describe the algorithms proposed in each stage. Firstly, a matching metric is defined to identify those points that belong to different images but are considered as homologous. The concept of homologous is also explained. Then, a grid or mesh based on these homologous points is defined. Finally, a non-linear transformation is computed to obtain the geometric transformation that put into spatial correspondence the source and reference image.

Two different approaches are implemented according to the dimensionality of the imaging studies. As in the singular point identification stage, there are two types of approaches: two-dimensional, applied only on one slice, and three-dimensional, which considers the whole imaging volume.

IV.2.4.2 Feature-based matching

Feature-based matching consists in finding corresponding singular points between pair of images. These corresponding singular points are named in this PhD homologous. In particular, two singular points are homologous, if the spatial and the feature vector distances are within a specific range. This stage is based on the graph and probabilistic theory and it is divided into three sub-stages: (I) k-d partitioning, (II) spatial analysis and (III) feature vector analysis.

Figure IV. 39 Feature-based matching stages.

In the first stage (I), space is partitioned into different quadrants. The first split (red) cuts the root space into two sub-cells, each of which is then split (blue) into two sub-spaces (shown in Fig.IV.40). Thus, the imaging volume is divided into different quadrants. The main goal of this stage is, on the one hand, to ensure that there are no mismatches through quadrants and, on the other, to minimize the impact of intensity abnormalities caused by brain injury. In the second

stage (II), the Euclidean distance of the spatial information (2: (x, y) or 3D: (x, y, z)) is computed. In the third stage (III), the similarity between the features vectors is analyzed by calculating the Euclidean distance. Those points fulfilling a minimum distance for both distances are considered homologous. Therefore, a pair of points are homologous in this PhD if the spatial distance and the vector of features of both point neighborhoods are within a specific range.

Figure IV. 40 K-d tree partitioning of imaging volume in two levels.

Two-dimensional approach

2D-BFRA computes the transformation between two images taking into account only homologous points, in other words, those singular points whose spatial and intensity characteristics are similar. Consequently, for the purpose of estimating the transformation between the two images, the target and the source image, only homologous points were used.

Each slice is divided, firstly, into four main quadrants. Both, spatial and feature-vector distances are computed between each quadrant. Then, the calculation of these distances is refined by dividing each main quadrant into four sub-quadrants. As previously mentioned, this K-d tree portioning approach allows mainly to diminish the number of mismatches.

Regarding the spatial distance, the objective is to find for each point of the target image which point of the source image (i) has the minimal distance and (ii) the distance is below a certain threshold (Th_s). The compliance of these two conditions ensures a one-to-one correspondence between the target and the source image. In other words, a bijective function exists between the two images. If the two conditions are met, these two points (one from the source image and one from the target image) are candidates to be considered as homologous (Eq.IV.20).

$$\begin{matrix} t_v = (xt_v, yt_v) \\ s_z = (xs_z, ys_z) \end{matrix} \text{ homologous if } d(t_v, s_z) = \min(d(s, t)) = \min(\sqrt{(xs_i - xt_j)^2 + (ys_i - yt_j)^2}) < Th_s \quad (\text{Eq.IV.20})$$

Where: $j = 1 \dots v \dots N$; $i = 1 \dots z \dots M$, N is the number of rows of the target image descriptor and M is the number of rows of the source image descriptor. Commonly M and N have different values.

Regarding the similarity among vectors of features from the source image (F_s) and the target image (F_t), we calculate the Euclidean distance among both vectors. The candidates are those points whose distance is smaller than a threshold (Th_f) (Eq.IV.21).

$$\begin{aligned} t_v &= (xt_v, yt_v) \\ s_z &= (xs_z, ys_z) \end{aligned} \text{ homologous if } d(Ft_v, Fs_z) = \sqrt{\sum_{i=1}^n (Fs_i - Ft_i)^2} < Th_f \quad (\text{Eq.IV.21})$$

The feature threshold, Th_f , is selected as the maximum of the accumulated distribution of the Euclidean distances among the vectors of features, as shown in Fig.IV.39. The accumulated distribution is computed by obtaining the Euclidean distance between each vector of features of the source image and each vector of features of the target image.

Figure IV. 41 Threshold for the distance of the feature vector between two images. The black line indicates the maximum of the distribution (Th_f value).

Only those points fulfilling both criteria, spatial and features similarity, are selected as homologous. Fig.IV.40 shows an example of automated selection of pairs of homologous points between a control subject slice and a LPBA40 atlas slice (Fonov et al. 2009). For display reasons, only 400 random pair of points and not around 1,500 have been shown. The left image is considered the template, whereas the right one is the source one.

Figure IV. 42 Feature-based matching stage. For visualization reasons only 300 random pair of homologous points have been shown

As it can be observed in Fig.IV.42, all corresponding-lines are parallel and join points that are located in equivalent quadrants. This is a visual measure to show that the number of mismatches, in other words, the number of false homologous pair of points is minimum. Section V analyzes the quality of the homologous points both quantitatively and qualitatively.

Three-dimensional approach

As in the 2D approach, 3D-BFRA computes the transformation between two images taking into account only homologous points. The volume is firstly divided into four quadrants, where the spatial and feature-vector distances are computed. In order to improve these distances, each main quadrant is divided into four sub-quadrants according to the K-d portioning approach.

The spatial distance is computed as in Eq.IV.22. Firstly, pairs of points with the minimal distance are detected and then, it is tested if this distance is below a threshold Th_s . This threshold is related to the size of the quadrants obtained in the previous stage (K-d tree portioning). If both conditions are met, these pairs of points are considered as homologous candidates.

$$\begin{aligned} t_v &= (xt_v, yt_v, zt_v) \\ s_p &= (xs_p, ys_p, zs_p) \end{aligned} \text{ homologous if } d(t_v, s_p) = \min(d(s, t)) = \min(\sqrt{(xs_i - xt_j)^2 + (ys_i - yt_j)^2 + (zs_i - zt_j)^2}) < Th_s \quad (\text{Eq.IV.22})$$

Regarding the feature-vector distance, the similarity among vectors of features from the source image (F_s) and the target image (F_t) is calculated by the Euclidean distance. Homologous candidates are those points whose distance is smaller than a threshold (Th_f), as in Eq.IV.23.

$$\begin{aligned} t_v &= (xt_v, yt_v, zt_v) \\ s_z &= (xs_z, ys_z, zs_z) \end{aligned} \text{ homologous if } d(Ft_v, Fs_z) = \sqrt{\sum_{i=1}^n (Fs_i - Ft_i)^2} < Th_f \quad (\text{Eq.IV.23})$$

The maximum of the accumulated distribution of the feature-vectors Euclidean distances is the threshold Th_f , similar to the distribution shown in Fig.IV.39. This distribution is computed by obtaining the Euclidean distance between each vector of features of the source image and each vector of features of the target image.

Only those points fulfilling both criteria, that is, those pair of points with minimal spatial distance and both, spatial and feature-vector distance below a threshold respectively, are selected as homologous. Fig.IV.41 shows an example of automated selection of pairs of homologous points between two control subjects (LPBA40 atlas slice (Fonov et al. 2009)). For

display reasons, only 300 random pair of points of around 82000 have been shown. The left volume is considered the template, whereas the right one is the source. All corresponding-lines are parallels and join points that are located in equivalent quadrants. Thus, the number of false homologous pair of points is minimum. This is analyzed in Section V.

Figure IV. 43 3D Feature-based matching stage. For visualization reasons only 300 random pair of homologous points have been shown

IV.2.4.3 Mesh Generation

The goal of this stage is to create a mesh, also named a grid, which covers the physical domain, in this PhD, the brain region. This mesh is the basis for calculating a vector displacement field to adapt the source image to the target one, as it is explained in the next subsection.

The main problem of mesh generation is to divide a physical domain with a complicated geometry into small and simple pieces, named elements (Shewchuk 1999). The points used to define the shape of the elements are called nodes. According to (Shewchuk 1999), a mesh must satisfy contradictory requirements:

- It must conform to the shape of the object or simulation domain.
- Its elements may be neither too large nor too numerous.
- It may have to grade from small to large elements over a relatively short distance.
- It must be composed of elements that are of the right shapes and sizes. In other words, the elements must be equilateral and equiangular.

The most common cell shapes, shown in Fig.IV.44, are categorized according to their dimensionality (2D and 3D) and type of elements. Generally, triangles and pyramids are more used than quadrilateral or prism cell shapes. This is due to the fact that they are the simplest polygons, quick and easy to create and they are most common in unstructured grids. An unstructured grid is a tessellation of the Euclidean space in an irregular pattern. This type of meshes are much more versatile because of their ability to combine good element shapes with odd domain shapes and element sizes that grade from small to large.

Figure IV. 44 Most common cell shapes

This PhD proposes to create a mesh based on the singular points detected in the previous stage. Although the detected points used to have a homogenous spatial distribution, it is necessary to have a list of the connectivity to specify the way a given set of vertices make up individual elements. Thus, the proposed mesh is categorized within unstructured mesh types.

In particular, homologous pairs of singular points are used to define a vector displacement field based on Delaunay triangular meshes. The defining property of a Delaunay triangulation is that no vertex of the triangulation lies in the interior of any triangle's circumscribing disk (unique circular disk whose boundary touches the triangle's three vertices) (Delaunay).

The main advantage of the Delaunay triangulation is that among all possible triangulations of a fixed set of points, it maximizes the minimum angle and optimizes several geometric criteria (Shewchuk 1999).

Two different distributions of paired singular points have been generated in the previous stage. A Delaunay triangulation is computed in the source and reference image, both meshes are composed of the same number of Delaunay triangles, consequently each triangle on the target mesh has its corresponding triangle on the source mesh.

Figure IV. 45. Example of Delaunay meshes. Top figure: 2D Delaunay approach. Bottom figure: 3D Delaunay approach.

The Delaunay triangulation algorithm, used to create these meshes, is subject to this pseudocode (John Augustine 2012):

Table IV. 1 Delaunay Triangulation pseudocode

Algorithm: DelaunayTriangulation(P)		
Input: a set P of n points in R^2 (2D) or in R^3 (3D)		
Output: a Delaunay triangulation of P .		
Step	2D	3D
1	Find the lexicographically highest point of P , in other words, the rightmost among the points with the largest y -coordinate.	
2	Find two points (p_{-1} , p_{-2}) in R^2 sufficiently far away and such that P is contained in the triangle $p_0 p_{-1} p_{-2}$.	Find three points (p_{-1} , p_{-2} , p_{-3}) in R^3 sufficiently far away and such that P is contained in the tetrahedron $p_0 p_{-1} p_{-2} p_{-3}$.
3	Initialize T as the triangulation consisting of the single triangle $p_0 p_{-1} p_{-2}$	Initialize T as the triangulation consisting of the single tetrahedron $p_0 p_{-1} p_{-2} p_{-3}$
4	Compute a random permutation $p_1, p_2, \dots, p_n$ of P	
5	for $r \leftarrow 1$ to n	
6	Find a triangle $p_i p_j p_k \in T$ containing p_r .	Find a tetrahedron $p_i p_j p_k p_h \in T$ containing p_r
7	if p_r lies in the interior of the triangle $p_i p_j p_k$	if p_r lies in the interior of the tetrahedron $p_i p_j p_k p_h$
8	then add edges from p_r to the three vertices of $p_i p_j p_k$, thereby splitting $p_i p_j p_k$ into three triangles	then add edges from p_r to the four vertices of $p_i p_j p_k p_h$, thereby splitting $p_i p_j p_k p_h$ into three tetrahedrons
9	else (p_r lies on an edge of $p_i p_j p_k$ or $p_i p_j p_k p_h$)	
10	Add edges from p_r to p_k and to the third vertex p_l of the other triangle that is incident to $p_i p_j$, thereby splitting the two triangles incident to $p_i p_j$ into four triangles.	Add edges from p_r to p_h and to the four vertex p_l of the other tetrahedron that is incident to $p_i p_j p_k$, thereby splitting the three tetrahedrons incident to $p_i p_j p_k$ into six tetrahedrons.
11	Discard p_{-1} and p_{-2} with all their incident edges from T	Discard p_{-1}, p_{-2} and p_{-3} with all their incident edges from T
12	return T	

With the objective of respecting faithfully the accuracy of the original information contained in the patient image studies and minimizing changes on them, patient image studies are selected as reference images, whereas atlas images are selected as source images. Selected atlas are composed of two types of studies: the usual anatomical MRI study and an anatomical segmented study. The first type is used to compute the transformation, the second one is transformed and it is used to identify injured neuroanatomical structures. Fig.IV.45 shows an

example of a 2D approach and a 3D approach. For display reasons all these meshes have been created with around a 10% of the total points.

IV.2.4.4 Non-linear transformation

The main goal of this section is to obtain a displacement field vector (DFV) to adapt the source mesh to the target one. This vector represents the displacement of each vertex of the source triangle respect to the target one. One of the main conclusions of the state of the art is that most landmark-based registration algorithms assume that a small is sufficient to register a set of images. In turn, brain lesions associated to brain injury may affect great and disperse areas. Therefore, the displacement field vector must ensures both small and great changes.

This PhD proposed to obtain the displacement field vector based on the signed area of a triangle. The signed area of a triangle is calculated as twice the area of the parallelogram defined by two sides of the triangle (Kimberling 1998). This signed area computes the relative position of each point inscribed into the triangle with respect to the vertices.

The following paragraphs describe the computation of the DFV according to the dimensionality: two-dimensional approach and three-dimensional approach.

Two-dimensional approach

The spatial location of each point inscribed into the source mesh triangles is weighted with their corresponding signed area (w_1, w_2, w_3) in the target mesh triangles. Each weight is a ratio between the area of the target triangle (v_0, v_1, v_2) and the area of the inscribed triangle (v, v_i, v_j ; where $i, j = 0, 1, 2$), as in Eq.IV.24.

$$w_1 = \frac{\begin{vmatrix} v_x - v_{2x} & v_{1x} - v_{2x} \\ v_y - v_{2y} & v_{1y} - v_{2y} \end{vmatrix}}{\begin{vmatrix} v_{0x} - v_{2x} & v_{1x} - v_{2x} \\ v_{0y} - v_{2y} & v_{1y} - v_{2y} \end{vmatrix}}, w_2 = \frac{\begin{vmatrix} v_x - v_{2x} & v_{0x} - v_{2x} \\ v_y - v_{2y} & v_{0y} - v_{2y} \end{vmatrix}}{\begin{vmatrix} v_{0x} - v_{2x} & v_{1x} - v_{2x} \\ v_{0y} - v_{2y} & v_{1y} - v_{2y} \end{vmatrix}}, w_3 = \frac{\begin{vmatrix} v_x - v_{1x} & v_{0x} - v_{2x} \\ v_y - v_{1y} & v_{0y} - v_{2y} \end{vmatrix}}{\begin{vmatrix} v_{0x} - v_{2x} & v_{1x} - v_{2x} \\ v_{0y} - v_{2y} & v_{1y} - v_{2y} \end{vmatrix}} \quad (\text{Eq.IV.24})$$

Where w_1, w_2 and w_3 are the weights; $v (v_x, v_y)$ is the point inscribed into the target triangle and $v_0 (v_{0x}, v_{0y}), v_1 (v_{1x}, v_{1y})$ and $v_2 (v_{2x}, v_{2y})$ are the vertices of the target triangles.

Fig.IV.46-A, B and C show how to obtain each weight and the graphic correspondence of the numerator (inscribed triangle, light blue area) and denominator (target triangle, dark blue area). As previously mentioned, each weight estimates the displacement of the source points to match the reference ones.

Fig.IV.46-D illustrates how the weights are applied to each source triangle vertex. The vertex of the source and target triangles are pairs of homologous singular points and hence, each vertex of the source has its correspondence vertex in the target triangle. This dual correspondence facilitates the computation of the new position of each source vertex while ensuring at the same time a low probability of distorting the image.

Figure IV. 46 Weight computation. A, B, C shows how the weights are computed and the graphical representation of the denominator and numerator. D illustrates how the source points (S0, S1, S2) are transformed to math reference points (V0, V1, V2).

The new position of each point inside the source triangle mesh (x' , y') is computed by weighting each vertex of the source triangle (s_0 , s_1 , s_2) with the weights (w_1 , w_2 , w_3) previously described, as in Eq.IV.25.

$$\begin{aligned} x' &= w_1 \cdot s_{0x} + w_2 \cdot s_{1x} + w_3 \cdot s_{2x} \\ y' &= w_1 \cdot s_{0y} + w_2 \cdot s_{1y} + w_3 \cdot s_{2y} \end{aligned} \quad (\text{Eq.IV.25})$$

When the spatial DFW has been calculated, the intensity values of the transformed source image are interpolated. There are different image interpolation algorithms as shown in (Prajapati, Naik & Mehta 2012). In order to introduce the minimum changes to the registered image, the most suitable algorithm is the nearest neighbor interpolation. This method does not introduce new intensity values to the image, it replicates intensity values of the neighbors of each interpolated pixel.

A simple proof of concept is shown in Fig.IV.47. Template and source images are similar phantoms but each of them contains a square of different size and position. Both squares are inscribed into a triangle whose vertex represents pairs of homologous singular points (left and central top figures), so there is a concrete correspondence among them, shown in the right top figure. The objective is to transform the source image to be as similar as possible. The displacement field vector is computed, as previously explained, and applied to the source image. Left bottom figure shows the difference between the source and the reference images, as we expect the only difference between them is the square. Central bottom figure shows the difference of the transformed source image, also named registered image, and the template one. As it is shown there is not a complete overlap mainly due to the size difference of both squares. Finally, left bottom figure shows the registered image showing that the original square has moved and resized to match the target one.

Figure IV. 47 Simple proof of concept of the proposed non-linear transformation algorithm.

Three-dimensional approach

As in the previous case, the goal is to calculate the transformation to match the source three dimensional mesh with the template one. Both meshes are composed of tetrahedrons whose vertex are pairs of homologous singular points. Therefore, all the points that compose either of the two meshes are associated. For simplicity, the goal of this sub-section is to transform the source tetrahedron (s_1, s_2, s_3, s_4) to be as similar as possible to a reference tetrahedron (v_1, v_2, v_3, v_4), as shown in Fig.IV.48.

Figure IV. 48 Transformation of the source tetrahedron to be as similar as possible to a template tetrahedron.

Each spatial location of each vertex is weighted with the signed volume (w_1, w_2, w_3, w_4). The signed volume contains information on how each point of the volume is related with each vertex of the polygon, in the case of this PhD, tetrahedrons. It is a ratio between the volume of the target tetrahedron (v_1, v_2, v_3, v_4) and the volume of an embedded tetrahedron (s_1, s_2, s_3, s_4), as in Eq.IV.26. The concept is similar to that of the two-dimensional approach.

$$\begin{aligned}
 w_1 &= \frac{\begin{vmatrix} v_x - v_{4x} & v_{2x} - v_{4x} & v_{3x} - v_{4x} \\ v_y - v_{4y} & v_{2y} - v_{4y} & v_{3y} - v_{4y} \\ v_z - v_{4z} & v_{2z} - v_{4z} & v_{3z} - v_{4z} \end{vmatrix}}{\begin{vmatrix} v_{1x} - v_{4x} & v_{2x} - v_{4x} & v_{3x} - v_{4x} \\ v_{1y} - v_{4y} & v_{2y} - v_{4y} & v_{3y} - v_{4y} \\ v_{1z} - v_{4z} & v_{2z} - v_{4z} & v_{3z} - v_{4z} \end{vmatrix}}, w_2 = \frac{\begin{vmatrix} v_{1x} - v_{4x} & v_x - v_{4x} & v_{3x} - v_{4x} \\ v_{1y} - v_{4y} & v_y - v_{4y} & v_{3y} - v_{4y} \\ v_{1z} - v_{4z} & v_z - v_{4z} & v_{3z} - v_{4z} \end{vmatrix}}{\begin{vmatrix} v_{1x} - v_{4x} & v_{2x} - v_{4x} & v_{3x} - v_{4x} \\ v_{1y} - v_{4y} & v_{2y} - v_{4y} & v_{3y} - v_{4y} \\ v_{1z} - v_{4z} & v_{2z} - v_{4z} & v_{3z} - v_{4z} \end{vmatrix}}, \\
 w_3 &= \frac{\begin{vmatrix} v_{1x} - v_{4x} & v_{2x} - v_{4x} & v_x - v_{4x} \\ v_{1y} - v_{4y} & v_{2y} - v_{4y} & v_y - v_{4y} \\ v_{1z} - v_{4z} & v_{2z} - v_{4z} & v_z - v_{4z} \end{vmatrix}}{\begin{vmatrix} v_{1x} - v_{4x} & v_{2x} - v_{4x} & v_{3x} - v_{4x} \\ v_{1y} - v_{4y} & v_{2y} - v_{4y} & v_{3y} - v_{4y} \\ v_{1z} - v_{4z} & v_{2z} - v_{4z} & v_{3z} - v_{4z} \end{vmatrix}}, w_4 = \frac{\begin{vmatrix} v_{1x} - v_{4x} & v_{2x} - v_{4x} & v_{3x} - v_{4x} \\ v_{1y} - v_{4y} & v_{2y} - v_{4y} & v_{3y} - v_{4y} \\ v_{1z} - v_{4z} & v_{2z} - v_{4z} & v_{3z} - v_{4z} \end{vmatrix}}{\begin{vmatrix} v_{1x} - v_x & v_{2x} - v_x & v_{3x} - v_x \\ v_{1y} - v_y & v_{2y} - v_y & v_{3y} - v_y \\ v_{1z} - v_z & v_{2z} - v_z & v_{3z} - v_z \end{vmatrix}}
 \end{aligned} \tag{Eq.IV.26}$$

Each of the four weights corresponds to the four vertex of a tetrahedron. The numerator corresponds to the volume of an embedded tetrahedron, whereas the denominator is computed as the volume of the template tetrahedron, graphically represented in Fig.IV.49.

Figure IV. 49. Three-dimensional weights. Graphic representation of each of the weights used to put into spatial correspondence two different tetrahedrons.

The new position of each point corresponding to the source mesh is calculated by weighting each vertex of the source tetrahedron with the four parameters, explained above, as in Eq.IV.27.

$$\begin{aligned}
 x' &= w_1 \cdot s_{1x} + w_2 \cdot s_{2x} + w_3 \cdot s_{3x} + w_4 \cdot s_{4x} \\
 y' &= w_1 \cdot s_{1y} + w_2 \cdot s_{2y} + w_3 \cdot s_{3y} + w_4 \cdot s_{4y} \\
 z' &= w_1 \cdot s_{1z} + w_2 \cdot s_{2z} + w_3 \cdot s_{3z} + w_4 \cdot s_{4z}
 \end{aligned} \tag{Eq.IV.27}$$

Intensity values of the new registered volume are obtained by interpolating. In particular, in order to not introduce new intensity values to the source image and be as conservative as possible, new intensity values are obtained by applying 'the nearest neighbor interpolation', as in the case mentioned above.

IV.2.4.5 Conclusions

This section describes the algorithms used to register the source and the target images. Thus, the objective of this stage is to put into spatial correspondence two different imaging studies. This stage is divided into three main stages: (A) feature-based matching, (B) mesh generation and (C) non-linear transformation.

This PhD proposes a two-dimensional (BFRA) and three-dimensional registration algorithm (3D-BFRA) based on spatial and intensity information. This is one of the main characteristics differentiating the algorithms proposed in this work from most of the algorithms existing in the state of the art, which allows to apply these algorithms to imaging studies of patients affected from brain injury. Since brain injury introduce important intensity abnormalities which make most state of the art algorithm to fail.

Another important characteristic of the proposed algorithms is that they permit to identify lesions on disperse areas. This is also very interesting as it permits to analyze the whole brain area or volume.

In order to introduce the minimal changes on the patient images, patient image studies are selected as reference images, whereas atlas images are selected as source images. This allows patient information to remain untouched.

These algorithms have been compared in Section V with the most important algorithms used on neuroimaging applications (Section III) and with two of the most important point set registration algorithms: ICP and CPC briefly explained at the beginning of this section.

IV.2.5. Brain lesion detection

IV.2.5.1 Introduction

The goal of last stage of the proposed methodology consists of analyzing the information of the registered image to identify those neuroanatomical structures with high probability of being injured.

As mentioned in Section III, in the state of the art, there are significantly less algorithms to identify brain injury lesions than to identify lesions associated with neurodegenerative diseases. According to one of the most important research TBI groups, there are three key research directions on the characterization of brain injury (TBI and stroke): quantitative measurements of TBI using new research tools; dynamic 3D imaging with multivariate information over time; and user-supervised, efficient, smart, flexible analysis, registration and parcellation. Both methodology and algorithms proposed in this PhD are related with these three key directions, as shown in Fig.IV.50.

Figure IV. 50 Key directions to identify brain injury lesions

In particular, this section is focused on the analysis of the registered images to identify those anatomical structures that may be injured with some probability according to a brain atlas. As mentioned in Section III, pathological changes on anatomical structures are always associated with intensity abnormalities and/or location alterations. This PhD proposes a methodology based on these two parameters: area or volume associated to intensity abnormalities and location.

Fig.IV.51 shows the proposed methodology to identify those anatomical structures whose area or volume (stage A) and location (stage B) have changed. Both parameters are compared in stage C and the probability of each anatomical structure to be injured is estimated. Finally anatomical structures whose area or volume and location are different from the normal ones are identified as injured (stage D). The normal parameters are estimated from an anatomical brain atlas. A text and visual report are generated not only with the identified anatomical structure but also with the probability of being injured.

Figure IV. 51. Lesion identification pipeline proposed in this PhD

The following paragraphs detail the algorithms used on each stage. Four different atlases are used to compare the results: LPBA40 (Fonov et al. 2009), IBSR18 (Internet Brain Segmentation Repository 2014), CUMC12 (Cardviews software 2014) and MGH10 (Nieto-Castanon et al. 2003).

IV.2.5.2 Area/Volume Difference map calculation

As previously mentioned, one of the main characteristics of brain injury on medical imaging studies is intensity alteration. The comparison of an original neuroanatomical atlas and a registered one permits to identify those structures whose area, in the two-dimensional case, or volume, in the three dimensional case, has changed.

Two-dimensional approach

In order to identify the structures whose area per slice has been modified as a consequence of a brain injury, three ratios are calculated: one of them belonging to the patient image, another one to the images of the control subjects used to create the atlas and the other one to the atlas which is used to identify the anatomical structures. These ratios allow to know the area of each of the anatomical structures segmented in the atlas in relation with the total area of the brain for each of the slices making up the imaging study volume. Eq.IV.28 corresponds to the partial ratio associated to the atlas, whereas Eq.IV.29 and Eq.IV.30 correspond to the partial ratio associated to the patient and control subject studies, respectively.

$$ratio(i,j)_{atlas} = \frac{area_{structure(i)}}{area_{brain}} \quad (Eq.IV.28)$$

$$ratio(i,j)_{patient} = \frac{area_{structure(i)}}{area_{brain}} \quad (Eq.IV.29)$$

$$ratio(i,j)_{control} = \frac{area_{structure(i)}}{area_{brain}} \quad (Eq.IV.30)$$

Where i indicates the number of the anatomical structure, for example in the atlas LPBA40 $i = 1 \dots 56$, as it segments 56 anatomical structures in total; and j indicates the number of slice within a volume.

The difference of ratio associated to the control subjects with the ratio of the atlas ($\text{diff}_{\text{control}}$) and that of the patient ratio with the atlas ($\text{diff}_{\text{patient}}$) are weighted with the inverse of standard deviation ($SD(i,j)$) of the area of each anatomical structure per slice (as in Eq.IV.31 and Eq.IV.32). This difference of ratio is named in this PhD area difference map.

$$\text{diff}_{\text{control}} = |\text{ratio}(i,j)_{\text{atlas}} - \text{ratio}(i,j)_{\text{control}}| * \frac{1}{SD(i,j)} \quad (\text{Eq.IV.31})$$

$$\text{diff}_{\text{patient}} = |\text{ratio}(i,j)_{\text{atlas}} - \text{ratio}(i,j)_{\text{patient}}| * \frac{1}{SD(i,j)} \quad (\text{Eq.IV.32})$$

Standard deviation is obtained by analyzing how the area of the different anatomical structures varies, by using the imaging studies of the control subjects used to obtain each one of the aforementioned atlases that are used in this PhD. Eq.IV.33 shows how to obtain the standard deviation, where $\bar{x}$ is the average value of the area per slice of each anatomical structure and x_i is the observed value of the area of each anatomical structure per slice.

$$\bar{x} = \frac{1}{N} \sum_{i=1}^N x_i; \quad SD = \sqrt{\frac{1}{N-1} \sum_{i=1}^N (x_i - \bar{x})^2} \quad (\text{Eq.IV.33})$$

This weight allows to take into account that an intensity variation in anatomical structures whose standard deviation is too high does not have to imply any damage on them, whereas it permits to focus on those anatomical structures whose standard deviation is small, since this means that they do not use to vary much and therefore a ratio difference on them indicates that there may have been any kind of lesion. An example of standard deviation is shown in Fig.IV.52, this standard deviation is obtained from the LPBA40 atlas, as it shows the cerebellum and the middle and inferior occipital gyrus present the highest values of the standard deviation.

Figure IV. 52 Standard deviation of each anatomical structure per slice of the LPBA40 atlas.

Fig.IV.53 shows an example of the proposed methodology to obtain the area difference map. This example corresponds to the control subjects.

Figure IV. 53. Proposed methodology to obtain the area difference map. Example that shows the calculation of the control subjects area difference map.

The threshold used to identify the structures that could be injured is obtained from the area difference map of the control subjects. In particular, 90% of the maximum of the control subjects different map is used as this threshold, as in Eq.IV.34.

$$\begin{aligned} diff_{patient} < 0.9 * \max(diff_{control}) & \text{ 'normal' structure} \\ diff_{patient} \geq 0.9 * \max(diff_{control}) & \text{ 'injured' structure} \end{aligned} \quad (\text{Eq.IV.34})$$

Fig.IV.54 shows how the threshold to detect those anatomical structures whose area has been modified is obtained. As it can be observed, the maximum of the area difference map is higher in the case of patients, since there is a greater variability regarding the area of those injured structures.

Figure IV. 54. Example of how to obtain the threshold to identify those neuroanatomical structures that may be injured based on the intensity.

Three-dimensional approach

In the three-dimensional approach, the intensity analysis is carried out taking into account the whole imaging volume. The methodology used in this approach is similar to the one explained previously. Firstly, the ratios to know the volume of each anatomical structure segmented in the atlas in relation with the total volume of the brain are calculated. Eq.IV.35, Eq.IV.36 and Eq.IV.37 correspond to the ratio associated to the atlas, control subjects and

patient, respectively. Where i indicates the number of the anatomical structure, for example in the atlas LPBA40 $i = 1... 56$, as it segments 56 anatomical structures in total; and j indicates the number of slice within a volume.

$$ratio(i,j)_{atlas} = \frac{volume_{structure(i)}}{volume_{brain}} \quad (Eq.IV.35)$$

$$ratio(i,j)_{patient} = \frac{volume_{structure(i)}}{volume_{brain}} \quad (Eq.IV.36)$$

$$ratio(i,j)_{control} = \frac{volume_{structure(i)}}{volume_{brain}} \quad (Eq.IV.37)$$

The main advantage of these volumetric ratios is that they minimize the impact associated to the area differences of the different anatomical structures according to the number of slice, since not all the imaging studies begin at the same head-height and therefore, this creates differences that may affect the results if these slices are taken independently. This is the main disadvantage of the two-dimensional approach. In turn, in the three-dimensional approach, given the total volume of the anatomical structure is analyzed, there is no need to take into account where it appears.

Fig.IV.55 shows an example associated to the superior frontal gyrus (right and left), as it can be seen (Fig.IV.55-A), this structure appears in a number of axial slices varying from 75 to 100 according to the control subject been analyzed. Hence, this structure presents different area values based on the number of the axial slice selected, as it is shown in Fig.IV.55-B.

Figure IV. 55. Advantage of volumetric ratios. A-Slices where the superior frontal gyrus appears in MRI-T1w studies of control subjects. B-Differences among the area value through different slices of a certain neuroanatomical structure.

As in the two-dimensional approach, the differences of the atlas ratio with the ratio of the patient and with the control subjects (as in Eq.IV.31 and Eq.IV.32) are weighted with the inverse of the standard deviation computed in Eq.IV.33. This weight permits to prioritize those structures with small standard deviation, as this means that a change on the volume of this structures means that they may be injured. These differences are named in this PhD, volume difference maps.

The criteria used to calculate the threshold is the same as in the two-dimensional approach (Eq.IV.34): the 90% of the maximum of the control subject's volume difference map is used as the threshold to determine which structures have change their volume, and thus may be consider as injured.

IV.2.5.3 Centroid location difference map computing

The other main characteristic of brain injury on medical imaging studies is the location alteration. As explained in the previous case of intensity alteration, the comparison of a registered atlas including the alterations presented on a certain patient with an original one, allows the identification of those structures that have change their position.

In order to identify location alterations, two location difference maps are computed: the first corresponds to the control subjects used to create the atlas (Eq.IV.38) and the other corresponds to the patient (Eq.IV.39). These two maps are based on the Euclidean distance between the centroids of the atlas (p_a) and the imaging studies of control subjects (p_c) and the patients (p_p); and they are weighted with the inverse of the standard deviation (Eq.IV.40), with the aim of giving more importance to those structures with small value of standard deviation, since this implies that they present a stable position on the study carried out with the control subjects of each atlas used in this PhD.

$$diff_{control} = \left| \sqrt{(p_x(i)_a - p_x(i)_c)^2 + (p_y(i)_a - p_y(i)_c)^2 + (p_z(i)_a - p_z(i)_c)^2} \right| * \frac{1}{SD(i)} \quad (\text{Eq.IV.38})$$

$$diff_{patient} = \left| \sqrt{(p_x(i)_a - p_x(i)_p)^2 + (p_y(i)_a - p_y(i)_p)^2 + (p_z(i)_a - p_z(i)_p)^2} \right| * \frac{1}{SD(i)} \quad (\text{Eq.IV.39})$$

$$\bar{p} = \frac{1}{N} \sum_{i=1}^N p_i; \quad SD = \sqrt{\frac{1}{N-1} \sum_{i=1}^N (p_i - \bar{p})^2} \quad (\text{Eq.IV.40})$$

Where $\bar{p}$ is the average location of a certain anatomical structure; and p_i is the location of the same anatomical structure in one control subject.

The threshold used to identify those structures whose location has been altered is obtain from the location difference map of the control subjects. This threshold, as in the previous case (area/volume difference map), takes the value of 90% of the maximum of the control subject difference map (Eq.IV.34).

Fig.IV.56 shows where the centroids of the 56 anatomical structures that make up the LPBA40 atlas are located and the standard deviation of their position. As mentioned in the previous intensity difference map, the analysis of the location of the anatomical structures' centroids may be performed in a two-dimensional and in a three-dimensional approaches. However, in this case the only difference to take into account is that in the two dimensional

approach the position of each centroid is computed as: $pos(i) = (x, y)$, whereas in the three dimensional approach the position is determined by the three space coordinates $pos(i) = (x, y, z)$.

Figure IV. 56 Example of centroid location of the LPBA40 atlas.

IV.2.5.4 Difference Map Comparator

The objective of this stage is to identify the neuroanatomical structures whose location or area/volume have changed and to establish the criteria to compute the probability of considering those anatomical structures as injured. Therefore, both difference maps: the area/volume and the centroid location are compared.

In order to reduce the number of false negatives, those anatomical structures which present any type of alteration, either in the area/volume difference map or in the centroid location difference map, are considered as structure candidate to be considered as injured.

Fig.IV.57 shows an example of the detection of anatomical structures whose area and location has been modified and therefore they are candidates to be defined as injured. As previously mentioned, those structures presenting any type of alteration: area or location, are considered as candidates. In this case, the three-dimensional registration approach has been used to calculate the deformation field that is applied on the atlas to detect the 'injured' anatomical structures. The detection of those anatomical structures with high probability of being damaged is performed in one slice to display the results in an easy way to see it. These

structures are displayed on the original image and are also gathered in a report, as it is explained in the next sub-section.

Figure IV. 57 Example of the identification of anatomical structures whose area and/or location has been modified based on the LPBA40 atlas.

With the aim of improving the information extracted from the imaging studies and giving a value of the probability that the anatomical structures may be injured, the tissue probability maps are computed by using the SPM segmentation algorithm (Ashburner, Friston 2003) and the atlas ICBM 152 (Fonov et al. 2011). Fig.IV.58 shows the workflow used to compute these probability values. Firstly, both patient and atlas image are segmented to obtain the GM, WM and CSF probability maps. Then each pixel is assigned to a certain tissue based on the maximum value obtained on each probability map in the 'Tissue mapping' stage. From the comparison of the two maps, it is obtained those areas and the probability of being damaged. As shown in this figure, the areas that are injured for sure appear in red color. These areas are associated to an anatomical structure based on the atlas segmented study used to identify the aforementioned injured anatomical areas.

Figure IV. 58 Workflow to assign an injured probability to a certain area.

IV.2.5.5 Injured anatomical structure identification

The goal of this final stage is to display the information obtained from the analysis of the images easily and effectively. Thus, this stage integrates the methods used to automatically generate the graphical and textual report.

The information relative to the anatomical structures detected in the previous stage is presented in two different ways: (1) visual and (2) text report, as shown in Fig.IV.57. The visual report integrates the original patient images with a map with those structures that have been detected. In particular, the map of the injured anatomical structures overlap the original image. In this way, the user can automatically identify which structures have been detected. The textual report consists of a list that contains: the numerical tag, name of anatomical structures including the hemisphere where it is located and the percentage of being injured, shown in Fig.IV.59.

Patient ID	Tag	Anatomical Structure	Injured Probability
	21	L superior frontal gyrus	84,2 %
	22	R superior frontal gyrus	82,1 %
	23	L middle frontal gyrus	75,6 %
	24	R middle frontal gyrus	79,4 %
	31	L lateral orbitofrontal gyrus	76,5 %
	32	R lateral orbitofrontal gyrus	80,6 %
	61	L superior occipital gyrus	48,2 %
	63	L middle occipital gyrus	42,6 %
	64	R middle occipital gyrus	58,9 %
	68	R cuneus	56,5 %
	81	L superior temporal gyrus	62,5 %
	82	R superior temporal gyrus	51,3 %
	83	L middle temporal gyrus	52,1 %
	84	R middle temporal gyrus	55,6 %
	87	L parahippocampal gyrus	59,6 %
	88	R parahippocampal gyrus	62,3 %
	89	L lingual gyrus	89,7 %
	90	R lingual gyrus	90,2 %
	101	L insular cortex	76,5 %
	102	R insular cortex	78,6 %
	122	R cingulate gyrus	45,5 %
	161	L caudate	85,3 %
	162	R caudate	87,6 %
	163	L putamen	91,2 %
	164	R putamen	90,5 %

Figure IV. 59 Example of graphical and textual report generation based on the LPBA40 atlas.

IV.2.5.6 Conclusions

This section describes the algorithms used to identify the anatomical structures whose area or volume and location have changed in relation a brain atlas of control subjects. This stage is divided into four main stages: (A) area/volume difference map computing, (B) centroid location difference map computing, (C) difference map comparator and (D) injured anatomical structure identification.

This PhD proposes a methodology to identify injured anatomical structures based not only on intensity but also on spatial location information. In order to identify damaged structures, it is necessary to characterize the atlas of control subjects. This characterization is based on the imaging studies of the control subjects used to create the atlas and permits to calculate the thresholds determining if an anatomical structure has changed its area or volume or its location. It also includes a value of the probability that the anatomical structure may be injured. This value of probability is based on the tissue information obtained from the calculation of the tissue probability maps. These maps (GM, WM and CSF) are computed with the SPM segmentation algorithm and the main characteristic of these maps is that each pixel is classified into GM, WM and CSF with a certain value of probability varying between 0 and 1. The maximum value of this probability indicates the belonging a type of tissue and it also is directly related to the probability that the neuroanatomical structure may be injured.

The information obtained from the analysis of the images is presented as a graphical and textual report.

These algorithms have been evaluated with different atlases following an assessment methodology proposed in this PhD and briefly described in Section V.

IV.2.6. Conclusions

Section IV describes the materials used in this PhD first. These materials are divided into medical imaging studies, brain atlases and development tools. Medical imaging studies are used to assess the proposed algorithms, in particular, MRI T1w studies of control subjects and brain injury patients (TBI and stroke). Brain atlases are used in most of the stages of the proposed methodology. All the algorithms have been implemented in MATLAB.

Then, the methods proposed in this research work is briefly described. The proposed methodology is divided into four main stages: (1) pre-processing stage, (2) singular points identification, (3) registration and (4) lesion detection.

The main goal of the **pre-processing stage** is to prepare the data to be processed and analyzed. This stage is divided into three main steps: skull-stripping, intensity normalization and spatial normalization.

In the first step, the scalp is removed from images because registration robustness is improved if 'non-brain parts' are eliminated. Two different approaches are described: automatic and semiautomatic. The automatic approach is based on the SPM segmentation algorithm and the semiautomatic approach is based on histogram analysis and region growing.

The intensity normalization stage adjusts the variation range of the histogram of each study to a common scale. This PhD uses an approach based on a histogram matching algorithm and a range intensity adjustment to intensity normalize imaging volumes.

The spatial imaging volumes are normalized regarding orientation and physical volume dimension. This stage is performed by using an algorithm based on the *reslice* algorithm of SPM. In the second stage, rigid structures are put into spatial correspondence. Three different approaches are described: a linear registration algorithm and two different point set registration algorithms (ICP and CPD).

Singular point identification stage aims to automatically identify singular points, also named landmarks, which are the basis for the registration algorithm, described below. The identification of singular points is divided into three main stages: (A) singular point location, (B) orientation assignment and (C) descriptor generation.

This PhD proposes a two-dimensional blob descriptor algorithm, named BFD. This algorithm adjusts SURF algorithm to the characteristics of MRI images. A volumetric extension of BFD, named 3D BFD, is also proposed.

In order to improve the subsequent registration process, this PhD proposes a multi-detector approach. In the case of the two-dimensional approach, three different type of features: edges (Prewitt), corners (Harris) and blobs (BFD) described each MRI slice. In the case of 3D, this PhD proposes to integrate an edge detector (3D Canny detector) with the 3D BFD.

The objective of the **registration stage** is to put into spatial correspondence two different imaging studies. This stage is divided into three main stages: (A) feature-based matching, (B) mesh generation and (C) non-linear transformation.

This PhD proposes a two-dimensional (BFRA) and three-dimensional registration algorithm (3D-BFRA) based on spatial and intensity information. Since brain injury introduces important intensity abnormalities which make most state of the art intensity based registration algorithms to fail, the combination of both spatial and intensity information allows to apply them to brain injury imaging studies.

In order to introduce the minimal changes on the patient images, patient image studies are selected as reference images, whereas atlas images are selected as source images. This allows patient information to remain untouched.

The objective of the **brain lesion detection stage** is to identify anatomical structures whose area or volume and location have changed in relation to a brain atlas of control subjects. This stage is divided into four main stages: (A) area/volume difference map computing, (B) centroid location difference map computing, (C) difference map comparator and (D) injured anatomical structure identification.

This PhD proposes a methodology to identify injured anatomical structures based not only on intensity but also on spatial location information. The information obtained from the analysis of the images is presented as a graphical and textual report.

The algorithms used and proposed in this section have been compared and evaluated in Section V.

V Results

In which the results obtained in each stage of the proposed methodology are briefly explained and discussed.

<" If a solution fails to appear ... and yet we feel success is just around the corner, try resting for a while. ... Like the early morning frost, this intellectual refreshment withers the parasitic and nasty vegetation that smothers the good seed. Bursting forth at last is the flower of truth." – Santiago Ramón y Cajal>

V.1. Results

This section describes and discusses the results obtained with the methods and algorithms described in Section IV. First, the assessment methodology for each of the stages of the methodology proposed in this PhD (shown in Fig.V.1) are described, then the results of each methodology are presented and discussed.

Figure V. 1 Methodology proposed in this PhD.

V.1.1. Assessment Methodology: Pre-processing Stage

The pre-processing stage proposed in this research work is divided into three main steps: (1) skull-stripping, (2) intensity normalization and (3) spatial normalization. In the first step, the brain is isolated from extra-cranial or ‘non-brain’ tissues. In the other two steps, the goal is to homogenize both the intensity variation window and the number of slices of each imaging volume and to put into the same spatial coordinate system all the imaging studies. Thus, the assessment methodology of the pre-processing stage evaluates on the one hand (A) the quality of two proposed skull-stripping algorithms and on the other hand (B), the normalization algorithms. Finally it globally evaluates the quality of the complete proposed workflow.

A. Materials

The dataset used to evaluate the performance of the proposed algorithms consists of a control structural MRI of the LPBA40 atlas. In particular, the data were used from a group of 40 control subjects of the LPBA40 atlas. LPBA40 is composed of 20 males and 20 females; the average age at the time of acquisition was 29.20 years, within the 19-40 age group; 56 structures were manually labeled according to custom protocols using BrainSuite software (Shattuck et al. 2008a).

In order to evaluate the semiautomatic algorithm, a seed point located in the middle of the imaging volume ($x/2, y/2, z/2$) has been used to generate the brain mask trying to minimize the variability associated to the election of that point.

B. Assessment Methodology: Skull-Stripping Algorithms

This assessment methodology is based on (Boesen et al. 2004). The objective is to evaluate the performance of the brain extraction algorithms. The proposed algorithms are applied on the original imaging studies and the obtained result are compared with the segmented ones.

The performance metric used is the *mean overlap (MO)* that describes the amount of overlap of voxels between the skull-stripped volume and the manual mask volume. This metric is calculated using the Dice similarity metric as in Eq.V.1, where S is the obtained skull-stripped imaging volume T is the manually segmented imaging volume.

$$MO = 2 \frac{|S \cap T|}{(|S| + |T|)} \quad (\text{Eq.V.1})$$

C. Assessment Methodology: Normalization Algorithms

The performance metrics used to assess the normalization algorithms are based on (Klein et al. 2009). In particular, the used metrics are:

- Target overlap (TO), is a measure of sensitivity defined as the intersection between the obtained (S) and the manually segmented (T) imaging volumes divided by the volume of the manually segmented volume, as in Eq.V.2.

$$TO = \frac{|S \cap T|}{|T|} \quad (\text{Eq.V.2})$$

- Mean overlap (MO), or SI, is defined as the intersection divided by the mean volume of the two imaging studies, as in Eq.V.3.

$$MO = 2 \frac{|S \cap T|}{(|S| + |T|)} \quad (\text{Eq.V.3})$$

- Union overlap (UO) or Jaccard coefficient, is defined as the intersection over the union, as in Eq.V.4.

$$UO = \frac{|S \cap T|}{|S \cup T|} \quad (\text{Eq.V.4})$$

V.1.2. Assessment Methodology: Singular Points Identification Stage

The goal of the assessment methodology in this stage is to evaluate the descriptor algorithms proposed in this PhD and to compare them with the algorithms of the state of the art. The methodology used to assess the proposed algorithms is based on (Luna et al. 2013) and (Mikolajczyk, Schmid 2005b).

As in the previous case, the dataset used to evaluate the performance of the proposed algorithms consists of a control structural MRIs of the LPBA40 atlas.

The parameters used to evaluate the algorithms are as follows:

- Execution time: the time during which the algorithms are running.
- Number of detected singular points: it represents the total number of detected singular points.
- General performance: it measures the number of singular points detected per second, as in Eq.V.5.

$$GP = \frac{\text{Number_detected_points}}{\text{Time}} \quad (\text{Eq.V.5})$$

• *Distribution of singular points:* it checks the homogeneity of the singular points distribution. This singular points distribution is based on the Delaunay triangulation. So this parameter takes into account the mean and the variance of the area of the Delaunay triangles whose vertex are the detected singular points. The more homogenous the distribution is, the bigger the area or volume covered by the detected singular points is. The homogeneity is measure based on the mean (Eq.V.6), where m_i is the value of each area or volume and N is the total number of samples; and variance (Eq.V.7).

$$\bar{m} = \frac{\sum m_i}{N} \quad (\text{Eq.V.6})$$

$$\text{Var}(m) = \sqrt{\frac{1}{N} \sum (m_i - \bar{m})^2} \quad (\text{Eq.V.7})$$

In order to find the best selection of imaging features to design the multi-detector approach, this research work analyzes the best combination of singular points detectors computing the average standard deviation of the Delaunay triangles of each mesh. In particular, four different slices of each subject to calculate how homogenous the distribution of the points in each mesh are. The smaller the standard deviation, the more homogenous the distribution of triangles in the mesh.

The assessment tests are classified in two-dimensional and three-dimensional. In the two-dimensional approach, the proposed algorithm BFD is compared with SIFT and SURF. In the three-dimensional approach 3D-BFD is compared with a 3D Canny detector.

V.1.3. Assessment Methodology: Registration Stage

Registration stage is divided into (A) feature-based matching, (B) mesh generation and (C) non-linear transformation. This evaluation methodology focuses, on the one hand, on assessing the matching and thus, the quality of the generated mesh, and on the other hand, on testing the registration algorithm.

A. Materials.

Three different imaging sets of control subjects have been used to assess the proposed algorithm. The first control structural MRI data were used from a group of 40 control subjects of the LPBA40 atlas. LPBA40 is composed of 20 males and 20 females; the average age at the time of acquisition was 29.20 years, within the 19-40 age group; 56 structures were manually labeled according to custom protocols using BrainSuite software (Shattuck et al. 2008a).

The second control structural MRI data were used from a group of 10 control subjects of the MGH10 atlas (Klein et al. 2009). MGH10 is composed of 4 males and 6 females; the average age at the time of acquisition was 25.3 years, within the 22-29 age group; 74 structures were manually labeled using Ghosh's ASAP software (Nieto-Castanon et al. 2003, Tourville, Guenther 2010).

The final control structural MRI data is composed of 12 control subjects (CUMC12) who were scanned at the Columbia University Medical Center. This images are from 6 males and 6 females within the 26-41 age group; 128 structures were manually labeled. These images were

resliced coronally to a slice thickness of 3mm, segmented and manually labeled by one technician trained according to the Cardviews labeling scheme (Caviness et al. 1996).

The registration algorithm is also analyzed by using an imaging patient dataset used to evaluate the algorithms proposed in the next stage: brain lesion detection. Patient structural MRI data were used from a group of 14 brain-damage patients. It was composed of 8 males and 6 females, average age was 46.64 ± 19.00 years

B. Quality of the matching.

Two imaging points appearing on two different images (reference and source) which share similar location and intensity neighborhood values, are considered as homologous, as it has been previously explained. On the one hand, the quality of the matching measures the spatial distribution of those points considered as homologous, as in Eq.V.6 and Eq.V.7; and on the other hand, the slope of the line connecting these two points (as in Eq.V.8) indicates the possibility of mismatching. The closer it gets to zero, the better the quality of matching is, since, regarding the spatial location, it means that the matching is correct between those points.

$$m_z = \frac{\Delta y}{\Delta x} = \frac{y_2 - y_1}{x_2 - x_1} \quad (\text{Eq.V.8})$$

The uniformity of the meshes evaluates if the matching stage improves the point distribution. This means that the mean (Eq.V.6) and variance (Eq.V.7) of the triangle mesh area should decrease. The homogeneity of the mesh has a direct impact on the vector displacement field quality, as this vector has more information about the regions to transform.

Finally, different spatial thresholds (Th_s) have been evaluated to analyze the better value to identify homologous points. ROC (receiver operating characteristic) space, explained below, permits to examine the results obtained by using different thresholds and to select the best value. In particular, we have tested distances from 1 to 60 pixels in 5 pixels steps. True positive rate (TPR) (Eq.V.9) and false positive rate (FPR) (Eq.V.10) are computed to evaluate the ROC space.

$$TPR = \frac{TP}{TP+FN} \quad (\text{Eq.V.9})$$

$$FPR = \frac{FP}{FP+TN} \quad (\text{Eq.V.10})$$

The quality of the mesh distribution is evaluated with the imaging dataset of the LPBA40 atlas.

C. Quality of the registration algorithm.

In order to carry out the assessment of the proposed registration algorithms, volume overlap measures are used to evaluate the performance of the proposed registration algorithm following the evaluation process suggested in (Klein et al. 2009). In particular, each of the brain images of each different dataset is registered to the other brain images of the same dataset. In other words, in the case of the LPBA40 atlas, each of the 40 brain images is registered to the 39 others. Thus, in total 1784 pairwise registration have been performed (1560 (LPBA40), 90 (MGH10) and 132 (CUMC12)).

Regarding the volume overlap measures previously mentioned, three different assessment parameters are used: the ‘*Target Overlap*’ (TO) measures the sensitivity of the methods (Eq.V.11) (Crum et al. 2005); the ‘*Dice coefficient*’ (DC) measures the mean overlap (Eq.V.12) (Zijdenbos et al. 1994) and the ‘*Jaccard Coefficient*’ (JC) measures the union overlap (Eq.V.13) (Gee, Reivich & Bajcsy 1993).

$$TO = \frac{\sum_{i=1}^N |S_i \cap T_i|}{\sum_{i=1}^N |T_i|} \quad (\text{Eq.V.11})$$

$$DC = 2 \frac{\sum_{i=1}^N |S_i \cap T_i|}{\sum_{i=1}^N (|S_i| + |T_i|)} \quad (\text{Eq.V.12})$$

$$JC = \frac{\sum_{i=1}^N |S_i \cap T_i|}{\sum_{i=1}^N |S_i \cup T_i|} \quad (\text{Eq.V.13})$$

Where $i = 1 \dots N$ is the number of labeled anatomical structures per slice, S is the source image and T is the target image.

To test quantitatively the utility of BFRA to identify lesions, we also compute DC and JC between the patient study and the registered atlas. However, in the case of the patient studies the volume overlap measures are brain-to-brain, as anatomical structures are not labeled on them, whereas in the case of the control subject studies the volume overlap measures are the average of the volume overlap per labeled anatomical structure.

V.1.4. Assessment Methodology: Brain Lesion Detection Stage

A. Materials

Patient structural MRI data were used from a group of 14 brain-damage patients. It was composed of 8 males and 6 females, average age was 46.64 ± 19.00 years. These MRI studies have been analyzed by a neurologist (Institut Guttmann), on a 1.5T Toshiba scanner and on a 1.5T Siemens scanner. Appendix A contains the mentioned evaluation of these studies.

Atlas ICBM 452 T1 (Mazziotta et al. 1995) is used in the pre-processing stage and atlas LPBA40 (Shattuck et al. 2008a) is used in the lesion detection stage.

B. Assessment of the detection algorithm

The objective of the assessment methodology in the last step of this PhD methodology: brain lesion detection stage, is to analyze the performance of the proposed brain lesion detection algorithm. This methodology is divided into three parts. Firstly, the general efficiency of the algorithm is assessed. Then, the ROC space is analyzed in detail and finally the area under the curve (AUC) is computed.

General efficiency (EFF) is defined as the ratio between number of detected brain structures (n_d) and the total number of neuroanatomical structures to be detected (n_t) by the algorithm, as in Eq.V.14. The total number of neuroanatomical structures is defined by the brain imaging study used as template.

$$EFF = \frac{n_d}{n_t} \quad (\text{Eq.V.14})$$

Regarding the analysis of the ROC space, these are the parameters computed to quantify the ability to identify lesions of the proposed algorithm: true positives (TP), true negatives (TN), false positives (FP), false negatives (FN), sensitivity (SEN) and specificity (SPE).

- True positives (*TP*). It indicates the presence of a condition when in reality it is present.
- True negatives (*TN*). It indicates the absence of a condition when in reality it is present.
- False positives (*FP*). It indicates the presence of a condition when in reality it is not present.

- False negatives (*FN*). It indicates the absence of a condition when in reality it is no present.

- Sensitivity (*SEN*). It is the probability to identify positive results whereas specificity relates the probability to identify negative results (Eq.V.15).

$$SEN = \frac{\sum \text{True positive}}{\sum \text{Condition positive}} = \frac{TP}{TP+FN} \quad (\text{Eq.V.15})$$

- Specificity (*SPE*). It measures the proportion of negatives that are correctly identified as such (Eq.V.16).

$$SPE = \frac{\sum \text{True negative}}{\sum \text{Condition negative}} = \frac{TN}{FP+TN} \quad (\text{Eq.V.16})$$

- Accuracy (*ACC*). It is the proximity of measurement results to the true value (Eq.V.17).

$$ACC = \frac{TP+TN}{TP+FP+FN+TN} \quad (\text{Eq.V.17})$$

The ROC curve depicts the trade-off between sensitivity and (1-specificity) of a classifier. The area under the curve (AUC) quantifies the effectiveness of the proposed algorithm to identify lesions. AUC measures how the proposed algorithms discriminate between injured anatomical structures and normal ones (Bradley 1997). The maximum value for the AUC is 1.0, indicating a perfect identification of hidden neuroanatomical structures. An area greater than 0.5 indicates that the algorithm can be used, as shown in Fig.V.2 (Fawcett 2006).

Figure V. 2 ROC space 2 (Fawcett 2006)

The area under ROC curve (AUC) measures how far the curve is from the base line. This area permits to qualify the algorithm in five different groups based on the quality of the classification. An example is shown in Fig.V.3.

- 0.90-1 = outstanding
- 0.80-0.90 = excellent
- 0.70-0.80 = acceptable (fair)
- 0.60-0.70 = poor
- 0.50-0.60 = no discrimination

Figure V. 3 Classification of an algorithm based on the AUC value (Fawcett 2006)

V.2. Pre-processing stage

V.2.1. Skull-Stripping Algorithms

The obtained results (see Fig.V.4) show that the automatic skull-stripping algorithm obtains a MO value of around 15% better than the semiautomatic algorithm. This is due to the fact that the seed voxel used to obtain the ‘brain-tissue’ mask in the semiautomatic algorithm is selected without taking into account if the intensity value is adequate or not. This means that the performance of the semiautomatic algorithm may increase if the user selects and controls the input parameters of the algorithm. However, with the aim of reducing the variability associated to user manipulation and of evaluating as objectively as possible this algorithm, this seed has been automatically selected.

Figure V. 4 Mean overlap of the automatic and semiautomatic skull-stripping algorithms

Fig.V.5 shows an example of one of the control subjects used to test these algorithms. In particular, it shows the original imaging volume, the manual mask used to compare and evaluate them and the results obtained with both algorithms. As it can be observed, the skull-stripped imaging volumes obtained contains most of the intensity information within the ‘brain region’ and the ‘non-brain region’ has almost fully been removed.

Figure V. 5 Example of an imaging volume study of one control subject of the dataset used to evaluate these algorithms. This figure shows three different slices (axial, sagittal and coronal) of the original MRI-T1w volume, a manual segmented brain mask and the volumes obtained with the automatic and semiautomatic algorithm.

In comparison with other algorithms used in the state of the art (shown in Fig.V.6), such as BSE (Shattuck et al. 2001), BET (Smith 2002a) and McStrip (Boesen et al. 2004), the automatic algorithm obtain a similar value of the mean overlap. It is important to take into account that the datasets used to evaluate the algorithms of the state of the art are different from the one used in this research work, so this comparison just want to give an idea about the quality of these algorithms regarding other similar algorithms.

Figure V. 6 Comparison of the proposed algorithms with the state of the art, although the datasets used to test the algorithms of the state of art are different from the ones used in this research work.

V.2.2. Normalization Algorithms

Following the assessment methodology proposed in V.1.1, Fig.V.7 shows the results obtained with the three algorithms explained in IV.2.2. This figure illustrates the average values and the 25th and 75th percentile of the distribution of the parameters used to assess the algorithms. The rigid registration algorithm is the one used in the proposed methodology as it obtains the best results, the TO is almost 1. This means that the overlapping between the registered and the target volume is nearly complete.

Figure V. 7 Comparison of the proposed algorithms used to normalize the imaging volumes.

The point set registration algorithms: CPD (Myronenko, Xubo Song 2010) and ICP (Bergström, Edlund 2014) used a corner detector based on the Harris detector to identify the points used to apply the registration algorithm. CPD obtains better results than ICP, this is mainly due to the fact that ICP algorithm assumes that every point of the target set corresponds with the closest point to it in the source set. However, CPD uses a probabilistic approach to align point sets based on the Gaussian mixture model (GMM) improving the obtained results.

The affine registration algorithm obtains better results than the CPD registration algorithm because of the distribution of the points used to compute the transformation. In particular, these points are only located over corners, so both the external contour and most of the internal areas corresponding to WM are not taking into account to calculate the rigid transformation. Whereas the affine registration is applied over the complete image so the transformation is considered as a global one and in terms of deformation, more changes are introduced in the image.

The results obtained with both point set registration algorithms may significantly improve if the algorithms used to identify these points take into account both intensity and spatial information and they correspond to different imaging features. This evaluation has been done in V.4 to test the proposed registration algorithm.

Fig.V.8 shows an example of the normalization algorithm over the same slice of the same subject, the areas where there are no overlap are represented in blue. This figure illustrates the

numerical results abovementioned, the affine registration algorithm obtains the best overlapping result compared with the other two point set registration algorithms.

Figure V. 8 Example of the normalization algorithms over a certain slice of a subject.

V.3. Singular points identification

V.3.1. Two-dimensional approach

Firs, an analytical studio to identify the best combination of imaging features is performed, as mentioned in Section V.1.2. Fig.V.9 shows the comparative among the different singular points detectors. The use of a single detector does not ensure a uniform distribution of the points. Nevertheless, it is important to emphasize that the standard deviation of the corner detector is much lower than the blob and edge detectors. This is because the corner detector computes singular points on brain areas with anatomical symmetry, so the distribution is more uniform than the blob and edge detector distributions. However, using the combination of the corner detector with the blob and edge detectors, the singular points are better distributed obtaining a more homogenous mesh and therefore a more reliable vector displacement field.

Figure V. 9 Comparative of singular points detectors. Each curve shows the right side of the normalized Gaussian distribution of the Delaunay triangles' area on four different slices of 40 different control subjects.

Regarding the execution time, as shown in Fig.V.10, BFD and SURF are practically identical. In both cases, it takes around 0.90 s. Nevertheless, SIFT takes longer. The main reason for this is that SURF and BFD use the integral image, whereas SIFT applies multiresolution on the image as explained in Section III. The execution time of the multi-detector approach is slightly higher than the time of SURF or BFD because this approach not only detects blob features but also edges and corners.

Figure V. 10 Execution time two-dimensional approach

As to the number of detected singular points (Fig.V.11), a significant difference is found among these descriptor algorithms. SIFT and SURF detect a similar average number of singular points, whereas BFD detects an amount of points significantly higher. This is due to the fact that BFD has been designed to detect blobs in MRI, as explained in Section IV. The average number of singular points detected by the multi-detector approach is the highest as it includes singular points corresponding to blob features, edges and corners.

Figure V. 11 Average number of detected singular points.

With regard to the performance (Fig.V.12), BFD and the multi-detector approach obtains the best results. In particular, the performance difference relative to SIFT and SURF is approximately 380%. This is mainly due to the fact that BFD and the multi-detector approach identify a higher number of singular points.

Figure V. 12 Descriptor performance

Singular points distribution indicates if the area covered by the points is homogenously distributed. The variance is the most significant indicator, since the smaller the variance is, the more homogenous the covered area is.

As shown in Fig.V.13, BFD obtains the better score of the variance and the mean area of each Delaunay triangle defined with the singular points is around 8 mm. This means that BFD identifies a high number of singular points and these points cover the brain area homogenously. SIFT and SURF identify less points and the distribution of the points does not cover the brain area uniformly.

The multi-detector approach also identifies a high number of singular points. However the variance is slightly higher than the BFD variance and the mean area of the Delaunay triangles is the lowest, so this means that the distribution of the points over the brain area is uniform although the variation of the area is more stable in the BFD case.

In conclusion, BFD and the multi-detector approach get the best results and hence, both approaches are suitable to be applied on MRI studies. However, as the final goal of these algorithms is to identify points on MRI T1w studies with intensity abnormalities, it is very important to detect different imaging features, as it permits to extract important information about different brain areas. This is the main reason why the multi-detector approach has been selected to apply on the singular points identification stage of the two-dimensional approach.

Figure V. 13 Singular points distribution

V.3.2. Three-dimensional approach

The execution time of the BFDA-3D is a 17% smaller than the time of the Canny-3D, as shown in Fig.V.14. As it happened in the two-dimensional approach, the main reason why there is this difference in the execution times is due to the use of the integral image and multiresolution in the case of BFD-3D.

Figure V. 14 Execution time three-dimensional approach

Regarding the number of singular points detected by both detectors, BFD-3D detects 8% more singular points, as shown in Fig.V.15. This is due to the fact that BFD-3D is designed by taking into account the characteristics of MRI studies, whereas Canny-3D has been designed to be applied on color images.

Figure V. 15 Average number of detected singular points

Therefore, the performance of the BFD-3D is higher than the Canny-3D ones, as shown in Fig.V.16. This is directly related to the fact that the number of singular points detected by BFD-3D is higher than the points detected by Canny-3D. It is important to take into account that Canny-3D has been designed for general purposes applications, whereas BFD-3D has been specially designed to be applied on MRI studies.

Figure V. 16 Descriptor performance – three-dimensional approach

Singular points detected by BFD-3D detector are distributed more homogeneously within brain volume, as shown in Fig.V.17. Both mean and variance of the Delaunay tetrahedrons volume are smaller in BFD-3D than in Canny-3D. This means that a mesh based on Delaunay, where the vertex of the tetrahedrons are the identified singular points is more uniform in the case of the BFD-3D, thus, the stability of the mesh obtained is higher and the results may be better.

However, it is interesting to identify different imaging features to obtain better results in the next registration stage. This is why both detectors are combined to be used in the registration stage, as explained in Section IV.

Figure V. 17 Singular points distribution

V.4. Registration

V.4.1. Matching algorithm

As previously mentioned, the quality of the matching has a direct impact on the results of the registration algorithm. For this reason, we first analyze the quality of the matching algorithm whose main goal is to identify those points located on two different images (reference and source) sharing similar spatial location and intensity distribution of the neighboring points. In the previous stage (singular points identification), the distribution of the detected singular points has been analyzed. As shown in Fig.V.18, the matching algorithm improves the obtained results in the stage of singular points identification. This means that both variance and mean of the area of the Delaunay triangles whose vertex are the homologous singular points, in the post-matching case, decrease around 20%. This happens due to the fact that only those points considered as homologous define each Delaunay triangle, so we assure that the spatial position of each vertex is the optimal one.

Figure V. 18 Singular points distribution. Comparative assessment between the results obtained without (pre) and with (post) applying the matching algorithm.

Regarding the slope of the line connecting these two points considered as homologous, we analyze the average values obtained by applying the approach based on the BFD algorithm and the multi-detector approach. In both cases, the values are close to zero. This means that the mismatching rate is minimum. As shown in Fig.V.19, it is the multi-detector approach the one obtaining the best result.

Figure V. 19 Average slope of the line connecting two homologous points.

Regarding the analysis of different values of the spatial threshold (Th_s), The threshold value obtaining better values in the ROC space is d6 (26 pixels), as shown in Fig.V.20. Both, the longer and the shorter distances obtain the worst curves. In the case of the shorter distance, this is due to the fact that the vector displacement field barely introduces spatial changes, so the registered image is too similar to the original one. In the case of the longer distance, more pairs of homologous singular points are wrongly identified. Therefore, despite the fact that the vector displacement field introduces greater spatial changes, the number of mismatches increases, meaning that not all the spatial changes are obtained according to real homologous points.

Figure V. 20 Representation of the ROC space to determinate the optimal spatial threshold Th_s for the matching stage. Distances from 1 to 60 pixels in 5 pixels steps have been tested.

V.4.2. Registration algorithm

We have computed and compared the volume overlap measures of the BFRA with the volume overlap measures presented by (Klein et al. 2009), where 14 different registration

algorithms were evaluated following the same evaluation process and the same control datasets briefly described in Section V.1.4.

According to the average values of the algorithms compared by (Klein et al. 2009), the proposed algorithm BFRA obtains better results in the three datasets. Fig.V.21 shows the target overlap, Fig.V.22 shows the Dice coefficient and finally Fig.V.23 shows the Jaccard coefficient.

Specifically, in the LPBA40 dataset, BFRA obtains a TO of 0.968 ± 0.004 , a JC of 0.948 ± 0.005 and a DC of 0.971 ± 0.002 , whereas the best algorithms of the aforementioned paper (ART and SyN) gets a TO of 0.719 ± 0.058 , a JC of 0.557 ± 0.069 and a DC of 0.715 ± 0.069 . Thus, BFRA increases the TO by 34%, the DC by 35% and JC by 70%.

In the MGH10 dataset, BFRA obtains a TO of 0.661 ± 0.095 , a JC of 0.404 ± 0.116 and a DC of 0.575 ± 0.096 . SyN gets a TO of 0.568 ± 0.128 , a JC of 0.395 ± 0.132 and a DC of 0.566 ± 0.134 . In this case, BFRA improves the TO by 16%, DC by 1% and JC by 2%.

Finally, in the CUM12 dataset, BFRA obtains a TO of 0.593 ± 0.067 , a JC of 0.398 ± 0.066 and a DC of 0.610 ± 0.063 . IRTK, SyN and SPM_D achieves similar results in this case. In particular, these three algorithms obtain a TO of 0.520 ± 0.139 , a JC of 0.379 ± 0.157 and a DC of 0.549 ± 0.107 . Thus, BFRA improves TO by 14%, JC by 5% and DC by 11%.

In conclusion, as shown in Fig.V.21, Fig.V.22 and Fig.V.23, BFRA improves the volume overlap measures obtained by the fourteen nonlinear registration algorithms compared by (Klein et al. 2009). This is due to the fact that the non-linear transformation is computed according to a grid whose vertex are the singular points identifies as homologous. Therefore, in order to calculate the transformation matrix BFRA takes into account not only intensity information but also spatial information. This has a direct impact on the quality of the results obtained not only with control subjects imaging datasets, but also with patients imaging dataset, as it is analyzed in the next section.

Figure V. 21. Target overlap by registration method between deformed source and target label images. According to (Klein et al. 2009): SPM_N* = 'SPM2-type' normalization, SPM_N = SPM's Normalize, SPM_US = Unified Segmentation, SPM_D = Dartel pairwise. The overlap values of all the nonlinear registration algorithms except BFRA in this paper have been obtained from (Klein et al. 2009).

Figure V. 22 Dice coefficient by registration method between deformed source and target label images. According to (Klein et al. 2009): SPM_N* = 'SPM2-type' normalization, SPM_N = SPM's Normalize, SPM_US = Unified Segmentation, SPM_D = Dartel pairwise. The overlap values of all the nonlinear registration algorithms except BFRA in this paper have been obtained from (Klein et al. 2009).

Figure V. 23 Jaccard coefficient by registration method between deformed source and target label images. According to (Klein et al. 2009): SPM_N* = 'SPM2-type' normalization, SPM_N = SPM's Normalize, SPM_US = Unified Segmentation, SPM_D = Dartel pairwise. The overlap values of all the nonlinear registration algorithms except BFRA in this paper have been obtained from (Klein et al. 2009).

Fig.V.24 shows two main stages of BFRA algorithm and the initial and final overlap. First, Fig.V.24-A shows the feature-based matching stage. For display reasons, only 300 random pair of singular points have been shown. The matching in some regions of the image around areas where there are significant variations in intensity requires that the movement needed to adjust those points is bigger than in regions without intensity variations or in control subject images. Fig.V.24-B shows the meshes of the source and target image. Finally, Fig.V.24-C shows a visual comparison between the initial and final overlap. Even though there are significant differences between the patient image and the atlas, BFRA improves considerably the overlap between them.

Figure V. 24 Two stages of the BFRA algorithm applied on a patient image and the initial vs final overlap. The top part of the figure (A) shows the feature-based Matching stage. For visualization reasons only 300 random pair of homologous points have been shown. The middle part of the figure (B) shows the target and the source mesh. The bottom part of the figure (C) shows the initial and final overlap qualitatively.

As mentioned in Section IV, we also compared the results of the proposed BFRA algorithm with two point set registration algorithms: CPD and ICP. As shown in Fig.V.25, BFRA achieves the best values of TO, JC and DC when these algorithms are applied on the LPBA40 atlas. These results highlight the potential used that point set registration algorithms may have on neuroimaging applications. BFRA obtains the best results due to the fact that it has been designed by taking into account the characteristics of MRI studies, however both ICP and CPD are registration algorithms of general applications, in other words, they are commonly applied on color (RGB) images. Thus, these two algorithms do not take into account spatial and intensity information.

Figure V. 25 Comparative assessment of BFRA and two point set registration algorithms (CPD and ICP)

Finally, in order to assess quantitatively the utility of BFRA to identify lesions, we have computed DC and JC of the brain-to-brain overlap among the patient dataset and LPBA40 atlas, as shown in Fig.V.26. Initially, the patient dataset has a DC of 0.82 ± 0.05 and a JC of 0.69 ± 0.05 . The SPM's normalize (SPM_N) (<http://www.fil.ion.ucl.ac.uk/spm/>) algorithm increases the initial overlap between the patients and the atlas images obtaining a DC of 0.85 ± 0.01 and a JC of 0.74 ± 0.01 . However, BFRA significantly improves the initial and the SPM value of DC obtaining a DC of 0.97 ± 0.01 and a JC of 0.94 ± 0.01 . This is mainly due to the fact that BFRA computes image transformations with anatomical meaning so, in the presence of lesions causing intensity variations, BFRA calculates the vector displacement field taking into account only those regions without variations.

Figure V. 26 Dice Coefficient for the patient dataset. First, the initial DC between the patient and the atlas image is computed (Initial DC). Then, we computed the DC of the BFRA and the SPM algorithm. The figure shows the average value of the DC and the first and third quartile.

V.5. Brain lesion detection

We should first mention that from the patient dataset described in subsection V.1.4, six patients have been ruled out as they do not present any brain injury in the selected MRI slices, as mentioned in the clinical assessment in Annex 1.

Regarding the ROC analysis, Fig.V.27 shows the value of TP, TN, FP and FN parameters on each of the evaluated patients. In all the cases, the number of VP matches the real number of anatomical structures that in the clinical assessment were identified as injured, so the number of FN is always 0. Therefore, our algorithm identified in all the cases the anatomical structures whose area or spatial location has changed.

In turn, the proposed methodology obtains a high value of FP. This is due to the fact that the algorithm categorizes as injured those structures that slightly change their area or location. This design decision is taken in order to minimize the FN value, as in most of the medical applications a high FN value indicates that an injury or an illness is not detected. Thus, it is preferable to ensure a void value of FN, although this means increasing the number of FP.

As mentioned in the Section VI, one of the proposed future works is a methodology based on artificial intelligence methods to decrease the number of FP.

Figure V. 27 ROC Analysis: TP (true positive), TN (true negative), FP (false positive), FN (false negative) - Brain lesion detection algorithm

Concerning efficiency, sensitivity, specificity and accuracy, the proposed algorithm obtains the maximum value in the first two parameters, as shown in Fig.V.28. This is due to the fact, that the number of FN is zero. This means that all the anatomical structures assessed as injured have been correctly detected. Specificity and accuracy values are lower due to the number of FP. Nevertheless, as previously explained, in medical applications it is preferable to ensure a void value of FN, although the number of FP increases.

Figure V. 28 ROC Analysis: EFF (general efficiency), SEN (sensitivity), SPE (specificity), ACC (accuracy) - Brain lesion detection algorithm

To sum up, Fig.V.29 shows the average value of efficiency, sensitivity, specificity and accuracy. The specificity obtains the lowest value due to the high number of FP. This high value also affects to the accuracy. Efficiency and sensitivity are the highest values that can be taken.

Figure V. 29 Summary: ROC Analysis EFF (general efficiency), SEN (sensitivity), SPE (specificity), ACC (accuracy)

By analyzing the ROC space, the proposed algorithm can be categorized as a good or bad brain injury detector. As shown in Fig.V.30, the obtained values of sensitivity and (1-specificity) locate the curve in the superior part and close to the point (0, 1). This point means that the algorithm makes a perfect discrimination between injured and healthy brain anatomical structures. According to this, the proposed algorithm is a good discriminator algorithm.

Figure V. 30 Categorization of the proposed algorithm based on the ROC Space

Another way of evaluating the proposed algorithm according to the quality of the identification of injured anatomical structures is the AUC. The proposed algorithm achieves a 0.89 AUC value, as shown in Fig.V.31, so the proposed algorithm is classified as an excellent discriminator of injured and healthy brain structures.

Figure V. 31 Categorization of the proposed algorithm based on the AUC

V.6. Conclusions

Section V describes first the assessment methodology used to evaluate each of the stages of the methodology proposed in this PhD. Results have been presented according to each of the stages of the proposed methodology: (1) pre-processing stage, (2) singular points identification, (3) registration and (4) lesion detection.

In the ***pre-processing stage***, the assessment methodology focuses on the evaluation of the skull-stripping and the normalization algorithms. Regarding the skull-stripping algorithms, the obtained results show that the automatic approach obtains a mean overlap value of around 15% better than the semiautomatic approach. In comparison with other algorithms used in the state of the art, although the dataset used to evaluate them is different from the used in the case of BSE and BET, the semiautomatic approach obtains a similar mean overlap value, whereas the semiautomatic approach achieves a slightly lower mean overlap value. This is mainly due to the fact that the seed voxel used to segment brain-tissue is automatically selected, so this seed does not take into account if the intensity value is adequate or not.

Regarding the normalization algorithms, the affine registration algorithm, used in the proposed methodology, obtains better results than the CPD and ICP registration algorithms because of the distribution of the points used to compute the transformation in each case. In particular, in case of the CPC and ICP, these points are only located over corners, so both the external contour and most of the internal areas corresponding to WM are not taking into account to calculate the rigid transformation. Whereas the affine registration takes into account the information contained in the whole image, in other words, transformation is considered as a global one and in terms of deformation, this means that it permits to introduce more changes to fit the source image to the target one.

In the ***singular points identification stage***, we have analyzed the best combination of detectors according to the distribution of these points on the image. The best combination is the multi-detector one, that has been the one used in the proposed methodology.

Then, we have compared the proposed descriptor approaches (BFD and multi-detector) with two of the most known algorithms. Regarding average number of detected singular points, performance and distribution, both BFD and the multi-detector approach achieves the best result in all the cases, so both approaches are suitable to be applied on MRI studies. However, as the final goal of these algorithms is to identify points on MRI studies with intensity abnormalities, it is very important to detect different imaging features as it permits to extract important information about different brain areas. This is the main reason why the multi-detector approach has been selected to apply on the singular points identification stage of the two-dimensional approach.

Regarding the evaluation of the 3D BFD (three-dimensional approach), we have compared the proposed algorithm with a 3D detector. The execution time of the proposed algorithm is 17% smaller, it detects 8% more singular points, the performance is 30% better and the distribution is 25% more homogenous than the ones achieved by the 3D detector of the state of the art.

In the ***registration stage***, we have evaluated the quality of the matching algorithm, since it has a direct impact on the results of the registration algorithm. The proposed registration algorithm (BFRA) has been compared with 14 different registration algorithms presented by (Klein et al. 2009). The matching algorithm improves the obtained results in the stage of singular points identification by 20%. This means that both variance and mean of the area of the Delaunay triangles whose vertex are the homologous singular points, in the post-matching case, decrease.

In the case of the LPBA40 dataset, BFRA increases the volume overlap measures (TO, JC and DC) by 34%, 35% and 70%, respectively. In the case of the MGH10 dataset, BFRA improves these measures by 16%, 1% and 2%. Finally, in the case of the CUM12 dataset, BFRA achieves a volume overlap measures improving by 14%, 5% and 11%. Therefore, the registration algorithm proposed in this PhD improves the volume overlap measures in all the datasets used.

We have also compared the results of the proposed BFRA algorithm with two point set registration algorithms: CPD and ICP. BFRA achieves the best values of TO, JC and DC when these algorithms are applied on the LPBA40 atlas. These results highlight the potential used that point set registration algorithms may have on neuroimaging applications. BFRA obtains the best results due to the fact that it has been designed by taking into account the characteristics of MRI studies, however both ICP and CPD are registration algorithms of general applications.

Finally, in the ***brain lesion detection stage***, we have assessed the quality of the methodology used to automatically identify which anatomical structures may be injured. In all the patient imaging studies, the number of VP matches the real number of anatomical structures that in the clinical assessment were identified as injured, so the number of FN is always 0. In most of the medical applications a high FN value indicates that an injury or an illness is not detected. Thus, it is preferable to ensure a void value of FN, although this means to increase the number of FP.

This methodology, obtains the maximum value of efficiency and sensitivity, as all the structures that have been manually evaluated as injured, have been correctly detected. Specificity and accuracy are lower due to the value of FP. As previously explained, in medical application, it is preferable to ensure a minimum value of FN, although this has a direct impact on the number of FP.

According to the analysis of the ROC space and the AUC value, the proposed automatic brain lesion detection methodology is categorized as an excellent detector of injured brain structures.

VI Conclusions and Future Works

In which the conclusions and main contributions of this thesis are presented and discussed based on the research hypotheses. In addition, possible future works to this thesis are contemplated.

<" In summary, all great work is the fruit of patience and perseverance, combined with tenacious concentration on a subject over a period of months or years." – Santiago Ramón y Cajal>

VI.1. Research hypotheses verification

The main conclusions from any PhD work are obtained by the acceptance or rejection of the research hypotheses based on the achieved results. In this chapter we analyze each of the hypotheses presented in Section II, assessing their degree of validity when confronted to our findings.

VI.1.1. General hypothesis

H1 – *The development of automatic methods for processing and analyzing medical imaging studies and the combination of them with techniques to classify extracted data, make it possible to automatically define the structural impairment profile of the patients.*

Hypothesis confirmed.

WHO estimates that TBI and stroke will become the leading cause of disability and will constitute two of the five major health challenges with the greatest impact on health policies by 2030. Both TBI and stroke affects the cognitive functioning directly, in particular, in 90% of the cases, these patients suffer from any type of impairment.

Neurorehabilitation aims to reduce the impact of the disabling conditions to reduce functional limitations and increase patient's autonomy. In order for the rehabilitation process to be more effective, treatments must be intensive, personalized to the patient's condition and evidence-based. Nowadays, there is a lack of knowledge regarding patient's disability profiles (cognitive or structural). For this reason, there is a need to design and develop new technologies to enhance the current brain knowledge in order to make these treatments follow the improvement conditions stated above. In particular, medical imaging studies may play an important role in the personalization and evidence-based design of neurorehabilitation treatments, since imaging studies contain information relative to the structural impairment profile.

This PhD proposes a complete methodology to pre-process, process and analyze medical imaging studies, in particular MRI T1w, to automatically identify brain lesions. This information may be mainly used for contributing to the cognitive dysfunctional profile and also to extract metadata used to create structured databases. The proposed methodology is divided into four stages representing the challenges dealt with in this research work.

The first challenge is to pre-process the imaging study in order to normalize them to a common intensity and intensity reference system. The pre-processing stage is critical to prepare the data to be processed and analyzed at the following stages. It is composed of three main steps: skull-stripping, intensity normalization and spatial normalization. Two different approaches (automatic and semiautomatic) are proposed and compared to eliminate the scalp from images in the skull-stripping step. In the intensity normalization step, this PhD applied an algorithm based on histogram matching and a range intensity adjustment. In the spatial normalization, an algorithm based on SPM is used to homogenize the imaging study regarding the volume dimensions and three different approaches are compared to align rigid structures.

The second challenge aims to identify singular points. These singular points are equivalent to the manual marking of points by the clinician. This PhD proposes two descriptor algorithms, BFD ('Brain Feature Descriptor') (two-dimensional) and 3D BFD (three-dimensional), which are adapted to be used on MRI studies. In order to improve the registration process, we propose the integration of these descriptor algorithms with other detectors resulting in a multi-detector approach.

The third challenge is to develop a registration algorithm to be used on MRI studies of ABI patients, where most of the current registration algorithms might not be suitable since brain lesions introduce topological differences associated with intensity and location alterations. This registration algorithm must also permit large deformations, as lesions associated to some strokes and TBI can affect great and disperse areas. This PhD proposes a registration algorithm based on descriptors, named BFRA ('Brain Feature Registration Algorithm').

The last challenge deals with the automatic identification of lesions. There are significantly less algorithms to identify brain injury lesions than to identify lesions associated with neurodegenerative diseases, as shown in Section III. However, three key research directions have been identified on the characterization of brain injury: quantitative analysis, multivariate information and flexible analysis. We have proposed a methodology based on these three key directions: the lesions are detected according to different types of information (intensity and spatial), the analysis is performed in the whole brain area and the algorithms permit to identify not only which anatomical structures have changed their area and location but also the probability of being injured.

VI.1.2. On the feature extraction of medical imaging studies

H2 – *The automatic classification and characterization of brain MRI studies permits to extract important information out of images which is not being used nowadays. In addition, it facilitates the improvement of the body knowledge associated with the neurorehabilitation by integrating multi-parametric information.*

Hypothesis partially confirmed

Nowadays, neurorehabilitation treatments are planned considering the results obtained from a neuropsychological assessment battery. Medical imaging studies are not used to design the treatment as there is a lack of automatic algorithms to identify anatomical structures that may suffer from alterations. However, in order to make rehabilitation treatments more effective, they must be intensive, personalized and evidence-based. It is these two latter features which medical imaging studies may use to enhance the information relative to the structural impairment of the patient. The results obtained in this research work prove that it is possible to extract automatically those anatomical structures that may be injured.

However, this information must be integrated in further research works to establish the usefulness of it. The result of these research works will validate or refute the second part of this hypothesis that is related to the improvement of the neurorehabilitation body knowledge.

H3 – *The combination of intensity variation information and spatial location information through descriptors permits to uniquely characterize a brain MRI study. The resulting information can also be considered as metadata in medical imaging database techniques.*

Hypothesis confirmed

Singular points are those points whose intensity characteristics are different from that of their neighbors. These singular points can be categorized as blobs, corners or edges. Many approaches have been proposed for extracting and organizing singular points. Descriptors are the most common algorithms used to detect and organize these points. These algorithms organize singular points in arrays, also named descriptors, where rows represent the number of detected singular points and columns contains the spatial location of the detected point and the vector of intensity features around their neighborhood. Therefore, descriptors combined intensity variation information (intensity features around the singular point neighborhood) and spatial location information. Each slice of an MRI study is characterized by a unique descriptor.

Medical imaging studies, such as MRI or CT, may be considered as intensity images. This means that they present important differences regarding imaging parameters that make them different from color images. Descriptors are commonly used with real world images or color words, so it is necessary to introduce changes in these algorithms to adjust the characterization of medical images. This PhD proposes two approaches of algorithms specially designed for MRI applications. The results show that the performance of the proposed algorithm is better than other algorithms designed for general purposes and they allow to describe each slice of the study in terms of imaging parameters.

H4 – *The use of descriptors in the field of medical imaging allows designing and developing a registration algorithm based on singular points. This registration algorithm works properly under intensity variation conditions within brain MRI studies.*

Hypothesis confirmed

Anatomical lesions introduce topological differences representing intensity abnormalities and/or location alterations. These alterations cause physical one-to-one correspondence between images not to exist due to the insertion or removal of imaging content. This inconsistency could severely reduce the performance of registration algorithms based on intensity imaging parameters.

As previously mentioned, brain injury modifies two parameters in medical imaging studies: the intensity and the location of imaging regions corresponding at least to one anatomical structure. Descriptors are algorithms integrating intensity and location information to detect singular points on images. As shown in Section III, registration algorithms based on descriptors have begun to be used on several medical imaging applications. This PhD proposes a registration algorithm based on descriptors to be used on ABI MRI studies. Throughout this research work, we have analyzed, evaluated and compared the proposed algorithms with

fourteen registration algorithms on different imaging datasets and with other two types of point set registration algorithms. In all the cases, we have improved the previous results.

VI.1.3. On the automatic lesion detection in brain injury patients

H5 – *Non rigid registration algorithm based on descriptors permits to detect and locate anatomical brain structures whose size or position have changed compared to the anatomical brain structures identified in an atlas of control subjects.*

Hypothesis confirmed

As mentioned in Section IV and in H1, there are significantly less algorithms identifying brain lesions associated to stroke or TBI than identifying lesions associated with neurodegenerative diseases. In order to develop a registration algorithm to identify lesions, there are three challenges that must be solved: (1) it must work under abnormal intensity characteristics, (2) it must permit to deform the image not only in disperse areas of the image and (3) it must allow large deformations, as lesions may produce huge imaging deformations. The non-rigid registration algorithms proposed in this PhD are based on descriptors. As mentioned in H4, we have designed and developed a descriptor algorithm according to the imaging characteristics of MRI studies. Descriptor algorithms aim to identify those points featuring special characteristics in the same way as a clinician manually delineate brain regions in order to establish an anatomical correspondence with atlases.

An anatomical structure is considered injured if the area/volume and/or the centroid position changes regarding an atlas. In order to identify which structures may be considered as injured, it is necessary to establish the normal range of variability of these structures (H6). As shown in Section V, the methodology proposed and the implemented algorithms permit to identify those anatomical structures that have changed these two properties with high efficiency and sensitivity, according to analysis of the ROC space.

H6 – *The statistical study of brain atlas permits to characterize anatomical structures on control subjects. Therefore, this statistical study allows to identify which anatomical structures have changed their area/volume and/or the position of their centroid with a reliability measure.*

Hypothesis confirmed

In order to identify anatomical structures, it is necessary to use brain atlas where these structures have been previously manually delineated. It is essential to establish the normality range of variation of each anatomical structure. As postulated in the hypothesis, statistical parameters characterize these anatomical structures allowing to identify those structures which are out of this normality range. This PhD proposes a methodology based on statistical parameters to analyze the atlas used to automatically identify anatomical structures that may be injured with a certain probability.

It is important to point out that this methodology permits to use any anatomical atlas where structures have been manually delineated. This means that our algorithms are independent from the used atlas of control subjects.

VI.1.4. On the quality evaluation of lesion identification

H7 – *The development of metrics to objectively assess the quality of the lesion identification provides significant information about the reliability of such identification.*

Hypothesis confirmed

Objective assessment metrics are essential not only to evaluate the quality of the identification of the injured structures, but also for the clinical user to know the integrity measure of the detection being carried out. Therefore, these metrics not only provide objectivity but also reliability to the information being extracted. Consequently, we consider that it is critical to develop assessment methodologies allowing to evaluate each of the main stages of the proposed methodology. In some cases, this has brought us to design adjusted methodologies to the type of medical imaging studies that have been used in this research work, always according to the state of the art.

VI.2. Main Contributions

Once the research hypotheses postulated have been validated, we now present the main contributions extracted from this PhD.

MC1. A complete methodology to pre-process, process and analyze MRI studies to identify anatomical structures that may be injured.

Neurorehabilitation is a complex clinical process used to restore, reduce and compensate the impact of disabling conditions, trying to improve the deficits caused by ABI in order to reduce the functional limitations and increase the individual's ability to function in everyday life. The body of knowledge of the neurorehabilitation discipline consists of (1) the relations among structural damage, (2) cognitive impairment profile and (3) clinical intervention results. The cognitive impairment profile is determined by neuropsychological assessment tests and the structural damage is obtained from clinical data of the patient.

However, currently, the relations between structural impairment and the cognitive impairment profile, or between them and the most appropriate rehabilitation tasks have not been established. In order to set possible correlations among these three types of information, it is necessary to develop tools enabling to quickly and easily identify anatomical lesions based on neuroimaging studies.

This methodology aims to facilitate the identification of possible correlations between cognitive impairment profile and structural impairment and to contribute to the unknown body of knowledge of the neurorehabilitation theory, as a previous step towards the personalized

therapeutic interventions based on clinical evidence. In particular, the main contribution of this PhD is to define and develop the structural impairment profile based on neuroimaging studies.

The methodology is divided into four main stages: pre-processing, singular point identification, registration and lesion identification. The main contributions on these stages are described in the following paragraphs.

This contribution is covered in detail in Section IV.1. The definition of the cognitive impairment profile associated with this methodology has led to contributions in international and national congresses.

MC2. The definition, development and validation of new descriptor algorithms to detect singular points on MRI studies.

Automated delineation of brain structures is a topic of great relevance in neuroimaging and neuroscience. Labelling regions is important to characterize the morphometry of the brain. However, in pathological conditions, handmade delineation of brain regions is the classical approach for establishing anatomical correspondence. This is an important methodological limitation as handmade labelling techniques suffer from inconsistencies within and across human labellers and are very time-consuming processes, hindering their extended use in clinical scenarios.

One of the main contributions of this PhD is the design, implementation and validation of a descriptor algorithm (two-dimensional and three-dimensional approach) used to automatically identify singular points on MRI studies. These singular points are the basis for the registration algorithm (MC3). The automated identification of singular points by descriptors represents (1) the automation of manual marking of landmarks by specialists, resulting in a release of time resources, (2) the increase of the number of landmarks, (3) the use of not only image intensity information but also anatomical information in the registration process, and (4) is a non-iterative process, so the computation time is a specific value.

The proposed algorithm has been compared with the descriptor algorithms most commonly used on medical and general applications to identify blob features. Results show that the performance of the proposed algorithm is better, making it more appropriate for its application within the framework of this research work.

These contributions are covered in detail in Section IV.2.3 and V.3. Publications derived from results include international and national congresses and a paper recently sent to an indexed scientific journal.

MC3. The definition, development and validation of a registration algorithm based on descriptors for computing nonlinear transformations under intensity abnormalities and their direct application to handle lesions on brain MRI studies.

Registration algorithms are the most common strategy for the identification of anatomical structures on brain studies. Brain lesions introduce topological differences associated with intensity abnormalities and/or location alterations. These differences become a great obstacle for image registration algorithms based only on intensity imaging parameters. Descriptors

integrate intensity and spatial information, thus the use of them improves the behavior of the registration procedure when there are intensity alterations. Registration algorithms based on descriptors have begun to be used on medical applications. However, we have not found any registration algorithm specifically used to identify lesions associated with stroke and TBI. Another of the main contributions of this PhD is a registration algorithm based on descriptors to identify brain lesions.

This proposed algorithm is validated by comparing it with thirteen nonlinear registration algorithms and three different control subjects' datasets. We also compare our algorithm with two point set registration algorithms to test the quality performance of it.

These contributions are covered in detail in Section IV.2.4 and V.4. Publications derived from results include international and national congresses and a paper recently sent to an indexed scientific journal.

MC4. The definition and validation of a methodology based on statistical parameters to characterize the normal variation range of anatomical structures manually delineated on brain atlas, and their application to identify those anatomical structures out of this range.

Pathological changes on anatomical structures are always associated with intensity abnormalities and/or location alterations. Thus, changes on area or volume and on the location of each anatomical structure previously segmented on an atlas are indicative that the structure can be injured. In this PhD, we have designed and implemented a methodology to statistically evaluate the area/volume and location of each of the anatomical structure segmented on the atlas. These statistical values are used as normality indicators and they make the identification of injured anatomical structures dependent on the selected atlas.

The methodology is designed to minimize the number of structures that, being injured, are not detected. Results show that in all cases the methodology allows to identify all the anatomical structures that the clinician classified as injured. Although the number of structures that, being normal, are considered as injured slightly increases. This affects directly to the specificity and accuracy of the algorithm. Finally, according to the AUC analysis, the algorithm is classified as excellent.

These contributions are described in detail in Section IV.2.5 and V.5. Results have been recently sent to an indexed scientific journal.

VI.3. Scientific Publications

VI.3.1. International Journals

J.M. Martínez-Moreno, P. Sánchez-González, **M. Luna**, T. Roig, J. M. Tormos, E. J. Gómez. Modelling Ecological Cognitive Rehabilitation Therapies for Building Virtual Environments in Brain Injury. *Methods of information in medicine* (2015).

VI.3.2. International Congress

- M. Luna**, B. Rodríguez-Vila, P. Sánchez-González, J. M. Tormos, E. J. Gómez. Automated Landmark Registration in Neuroimaging. *International Journal of Computer Assisted Radiology and Surgery*, 10(1), (2015).
- I. A. Yassine, **M. Luna**, B. Rodríguez-Vila, J. M. Tormos, E. J. Gómez. Content-based image retrieval system for brain magnetic resonance imaging based on pseudo-zernike coefficients combined with wavelet features. *International Journal of Computer Assisted Radiology and Surgery*, 10(1), (2015).
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- M. Luna-Serrano**, F. Gayá Moreno, P. Sánchez-González, C. Cáceres, A. Pascual-Leone, J. M. Tormos Muñoz, E. J. Gómez Aguilera, Brain structures identification based on future descriptor algorithm for Traumatic Brain Injury. *International Conference on Recent Advances in Neurorehabilitation (ICRAN 2013)*, pages 171-174, (2013).
- M. Luna-Serrano**, R. Caballero-Hernández, L.M González Rivas, A. García Molina, A. García Rudolph, C. Cáceres, R. Sánchez Carrión, T. Roig Rovira, J. M. Tormos Muñoz, E. J. Gómez Aguilera. Dysfunctional 3D model based on structural and neuropsychological information. *International Conference on Recent Advances in Neurorehabilitation (ICRAN 2013)*, pp. 175-178, (2013).
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M. Luna, Francisco Gayá, César Cáceres, Josep M. Tormos, Enrique J. Gómez. Evaluation Methodology for Descriptors in Neuroimaging Studies. VISAPP 2013 - Proceedings of the International Conference on Computer Vision Theory and Applications, pp. 114-11, (2013)

VI.3.3. National Congress

M. Luna Serrano, R. Caballero Hernández, P. Chausa, A. García Molina, J. M. Tormos, E.J. Gómez, Perfil cognitivo disfuncional de pacientes con daño cerebral adquirido basado en modelos neuropsicológicos y en estudios de imagen médica. *CASEIB 2014 XXXII Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, (2014).

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P. Sánchez-González, **M. Luna Serrano**, A. Fernández Pérez, I. Oropesa García, J. A. Sánchez Margallo, F. M. Sánchez Margallo, E. J. Aguilera. Métodos de segmentación y seguimiento de estructuras para video laparoscópico. *CASEIB 2011 XXIX Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, (2011).

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M. Luna Serrano, F. Gayá, J. M. Tormos Muñoz, E. J. Gómez Aguilera. Detección automática de puntos singulares en imágenes de resonancia magnética cerebral. *CASEIB 2011 XXIX Congreso Anual de la Sociedad Española de Ingeniería Biomédica*, (2011).

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M. Luna Serrano, S. Bashir, C. Cáceres Taladriz, J. M. Tormos Muñoz, E. J. Gómez Aguilera. Aportaciones del guiado estereotáctico sin marco a la Estimulación Magnética Transcraneal con

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VI.3.4. International seminars

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VI.4. Future works

The research work carried out in this PhD leaves an open door to new research lines related to the main challenges addressed in this work. Some of the proposed future works are described in the next paragraphs.

VI.4.1. Concerning pre-processing algorithms

Pre-processing algorithms are fundamental to prepare the data to be processed and analyzed in further stages. This PhD reviews the proposed algorithms to remove the scalp from the MRI studies in order to improve registration results, to establish a common intensity reference for all the studies used under the proposed methodology and to spatially normalize the imaging studies where rigid structures are aligned. Therefore, these are the future research works may be developed.

Design and development of a skull-stripping algorithm based on a Bayesian framework.

With the aim of enhancing the removal of the scalp, having a direct repercussion on the improvement of further processing algorithms, we propose to introduce segmentation algorithms based on a Bayesian framework. These algorithms are commonly used on tractography images and they permit to segment different tissues. They are based on the assumption that each tissue can be previously modelled. In the case of the scalp, there are certain characteristics that make possible to generate a model, since it is always located in the outside part of the brain area of the image and it presents high intensity levels.

Use of the proposed registration algorithm in the spatial normalization stage.

As the proposed registration algorithm of this research work obtains good results in imaging studies of ABI patients, we also proposed to use it on the spatial normalization stage to establish the relation matrix between the external points of the mesh generated with the points that have been identified as homologous. The main advantages of this type of spatial normalization are ensuring the use of spatial and intensity information to put into correspondence two images and the fact that the transformation is applied globally, so each region of the source image are adapted to the reference image.

VI.4.2. Concerning the identification of singular points

Design and development of descriptor integrating a multi-detector approach.

The identification of singular points allows to automatically label anatomical regions corresponding to anatomical structures. These singular points, also named imaging features, may be obtained from the hessian matrix, where eigenvectors and eigenvalues determine the type of local feature. A descriptor, as explained through this research work, is an algorithm that not only integrates a detector but also extracts information out of the neighboring areas of each detected singular point. Thus, descriptors not only contain spatial information but also intensity gradient information of each singular point's neighboring area. A future work is to design and develop a descriptor that integrates more than one type of descriptor and hence, we could have a multi-detector approach in only one algorithm. This research is being dealt with by D. Francisco Gayá Moreno, in the framework of his PhD in the Bioengineering and Telemedicine Center of the Universidad Politécnica de Madrid.

Design and development of a content-based image retrieval system based on the proposed descriptors.

The information relative to singular points is used on the registration algorithm. However, a content-based image retrieval (CBIR) system could be implemented based on the descriptor information. This type of system permits to store and classify medical imaging studies in a world where big data is a reality.

VI.4.3. Concerning registration algorithms

Design and implement the iterative stage of the proposed nonlinear registration algorithm based on descriptors.

The proposed algorithm is non iterative, as the transformation matrix is computed in one step. However, when the injury has produced a great deformation on a certain brain area, although the proposed algorithm simulates this imaging change, an iterative stage will improve these results. Since a similarity metric will determinate when the transformation matrix produce a result that fulfills established requirements. These requirements may be automatically set up or may be defined by the user.

VI.4.4. Concerning the identification of lesions

Designing and developing an intelligence artificial stage to train the proposed lesion detection algorithm in order to reduce the number of false positives.

As previously mentioned, the proposed methodology to automatically identify lesions is designed to minimize the value of false negatives. However, this affects directly to the specificity and accuracy of the algorithm as it increments the value of false positives. Although the proposed algorithm is classified as excellent according to the AUC analysis, the design of an intelligence artificial stage will improve these parameters, since the algorithm could be trained with cases supervised by clinicians. Thus, the algorithm will learn the cases in which an anatomical structure is finally defined as injured and the value of false positives will decrease.

VI.4.5. Concerning the evaluation

Extension of the patient database to improve the statistical significance of the results.

The greater the database is, the more statistical significance the results will be. For the last two years, European and American research consortiums have been developing not only new tools to be used on stroke and TBI patients, but also new open databases to be used on research projects. It would be interesting to test our algorithms on these databases.

Integration of the structural impairment profile on the cognitive dysfunctional profile to evaluate the usefulness of this type of information when designing and evaluation neurorehabilitation treatments.

The definition of the cognitive dysfunctional profile has a direct impact on the personalization of the rehabilitation treatments. Nevertheless, in order to assess the usefulness of this profile, it is necessary to introduce it in real clinical procedures. The comparison of rehabilitation treatments designed based on this profile and on the current parameters will establish the real utility of this new concept of dysfunctional profile.

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Glossary of acronyms

Acronym	Definition
A	
ABI	Acquired Brain Injury
ADC	Apparent Diffusion Coefficient
ADNI	Alzheimer Disease Neuroimaging
AIR	Automatic Image Registration
ANIMAL	Automatic Nonlinear Image Matching and Anatomical Labeling
ANTs	Advanced Normalization Tools
ART	Automatic Registration Toolbox
AVMs	Arteriovenous Malformations
B	
BFD	Brain Feature Descriptor
BFRA	Brain Feature Registration Algorithm
BIAUSA	Brain Injury Association of America
BRIEF	Binary Robust Independent Elementary Features
BRISK	Binary Robust Invariant Scalable Keypoints
C	
CC-FFD	Correlation coefficient - Free form deformation
CDE	Common Data Elements
CenSurE	Center Surround Extremas
CER	Comparative Effectiveness Research
CIHR	Canadian Institutes of Health Research
CNS	Central Nervous System
CPD	Coherent Point Drift
CSF	Cerebrospinal Fluid
CT	Computed tomography
D	
DFV	Displacement Field Vector
DoG	Difference of Gaussians
DRAMMS	Deformable registration via attribute matching and mutual-saliency weighting
DROP	Dense image registration through MRFs and efficient linear programming
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
E	
EC	European Comission
EM	Expectation Maximization
ETSIT-UPM	Escuela Técnica Superior de Ingenieros de Telecomunicación

Acronym	Definition
F	
FAST	Features for Accelerated Segment Test
FLAIR	Fluid-Attenuated Inversion Recovery
FLIRT	Linear Image Registration Tool
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FS	Filter Size
FREAK	Fast Retina Keypoint
G	
GBT	Bioengineering and Telemedicine Center (Grupo de Bioingeniería y Telemedicina)
GCS	Glasgow Coma Scale
GLOH	Gradient Location and Orientation Histogram
GM	Gray Matter
GMM	Gaussian Mixture Model
GRE	Gradient Echo
G-SURF	Gauge SURF
H	
HBP	Human Brain Project
HOG	Histograms of Oriented Gradients
I	
ICBM	International Consortium For Brain Mapping
ICH	Intracerebral Hemorrhage
ICP	Iterative Closest Point
ICT	Information and Communications Technology
ICU	Intensive Care Unit
InTBIR	International Initiative for Traumatic Brain Injury
IRTK	Image Registration Toolkit
J	
JRD-fluid	Jensen-Rényi Divergence
L	
L	Linear
LESH	Local Energy based Shape Histogram
LoG	Laplacian of Gaussians
LS	Lobe Size
M	
MALP-EM	Multi-atlas label propagation with expectation-maximization based refinement
MEG	Magnetoencephalography
MI-FFD	Mutual information – Free form deformation
MNI	Montreal Neurological Institute

Acronym	Definition
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MRSI	Magnetic Resonance Spectroscopic Image
MSER	Maximally Stable Extremal Regions
MTL	Medial Temporal Lobe
N	
NIH	National Institutes of Health
NL	Non Linear
O	
OASIS	Open access series of imaging studies
OCT	Optical Coherence Tomography
OCT	Octave
ORB	Oriented FAST and Rotated BRIEF
P	
PCA	Principal Component Analysis
PCBR	Principle Curvature-based Region detector
PET	Positron Emission Tomography
PhD	Philosophiæ Doctor
R	
RIFT	Rotation Invariant Feature Transform
ROI	Region of Interest
ROMEO	Robust multilevel elastic registration based on optical flow
RRI	Responsible Research and Innovation
S	
SAH	Subarachnoid Hemorrhage
SCL	Scale Level
SD	Standard Deviation
SIFT	Scale Invariant Feature Transform
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
SSD	Sum of Squared Differences
SSD-FFD	Sum of squared difference – Free form deformation
SURF	Speed Up Robust Feature Transform
SUSAN	Smallest Univalued Segment Assimilating Nucleus
SyN	Symmetric Image Normalization Method
T	
T1W	T1 Weighted
T2W	T2 Weighted
TBI	Traumatic Brain Injury

Acronym	Definition
U	
UCLA	University of California (Los Angeles)
UPM	Universidad Politécnica de Madrid
US	Ultrasound
V	
VBM	Voxel-Based Morphometry
W	
WCE	Wireless Capsule Endoscopy
WHO	World Health Organization
WM	White Matter
WOS	Web of Science