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Memory functional connectivity study in patients with temporal lobe epilepsy

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Resumo

A Epilepsia do Lobo Temporal (TLE) pode causar deterioração da memória em pacientes e estima-se que seja responsável por cerca de 40% de todas as epilepsias em adultos. Sendo uma das epilepsias mais comuns, é resistente a medicamentos em 76,8% dos casos, necessitando, portanto, de cirurgia.

A cirurgia continua a ser uma opção essencial para o tratamento da TLE farmacologicamente intratável. O principal objetivo da cirurgia de epilepsia é a remoção cirúrgica completa do foco epileptógeno com pouco impacto em funções como a memória. No entanto, apenas 66% dos pacientes consegue ficar livre das crises pós-operatórias e mais de 30% dos pacientes sofrem de declínio da memória.

Imagens funcionais do cérebro podem ser usadas para explorar padrões cerebrais anormais observados na epilepsia. Através da ressonância magnética funcional (fMRI) já se verificou que existe a reorganização das redes de aquisição da memória dentro do lobo temporal na TLE. Qualquer aplicação clínica de fMRI envolve um paradigma, uma medida funcional definida e uma tarefa que provavelmente ativará a área cortical de interesse. Os estudos de fMRI apresentam um conjunto único de parâmetros de desenho que precisam ser demonstrados. O desenho experimental de um estudo de fMRI é complexo porque envolve questões importantes relacionadas com experiências psicológicas e também questões relacionadas com a aquisição de dados e apresentação de estímulos. O fato é que diferentes estudos e autores produziram diferentes desenhos experimentais no sentido de otimizarem os seus resultados estatísticos, e a conclusão que se pode tirar é que algumas intuições e testes de otimização do design podem ser obtidos a partir de uma compreensão mais aprofundada da análise estatística de dados de fMRI.

Devido à possibilidade de observar diferentes áreas de atividade do cérebro através de fMRI, obtendo assim informações valiosas para estudar a disfunção da rede de memória, este projeto visa determinar a rede de memória em indivíduos com epilepsia do lobo temporal através de uma regressão de respostas de inferência fornecidas pelos próprios pacientes.

Paradigmas de memória convencionais requerem instrumentação complexa e/ou cara, impedindo a sua adoção mais ampla. Portanto, um paradigma de memória envolvendo abrir e fechar de mãos (aperto de mão) foi adotado aqui para recolher o feedback do paciente sem os referidos constrangimentos.

A TLE é uma condição neurológica crónica caracterizada por crises epiléticas recorrentes. É a região mais epileptógena do cérebro humano. Como a TLE é definida pela perda de células e gliose no hipocampo, córtex entorrinal e amígdala, que estão envolvidos na aquisição, armazenamento e

recuperação da memória, é crucial entender e determinar a rede de memória em pacientes com TLE através de fMRI.

Pacientes e Paradigma: Foram estudados 12 pacientes com TLE com idades compreendidas entre os 25 e 62 anos. Como parte de um protocolo de planeamento pré-cirúrgico, todos os pacientes realizaram um paradigma de abrir e fechar de mãos e um paradigma de memória de rosto-nome adaptado e apresentado usando o PsychoPy.

Um desenho em blocos com a duração de 100 segundos foi usado para o paradigma de abrir e fechar de mãos onde se pediu aos pacientes para mover alternadamente cada mão por 10 segundos.

O paradigma da memória consistiu em visualizar rostos desconhecidos para o paciente emparelhado com nomes fictícios, num desenho modificado de Novo vs. Repetido, com duração total de 10 minutos. Cada par rosto-nome foi apresentado durante 5 segundos. Um total de quatro séries foram feitas, em que cada série era composta por pares de rosto-nome novos seguidos por uma cruz de fixação para descanso, seguido por pares de rosto-nome repetidos. Os pares de rosto-nome repetidos podiam ter nomes errados associados para verificar se o paciente se lembrava do par correto. A resposta dos pacientes foi fornecida através do abrir e fechar de mãos (mão esquerda para FALSO / mão direita para VERDADEIRO).

Aquisição de fMRI: Os scans do cérebro foram feitos usando um equipamento de ressonância magnética de 1,5T com uma bobina de matriz de cabeça de 12 canais. Um scan volumétrico ponderado em T1 foi feito para cada paciente, seguido de sequências de imagem de contraste dependente do nível de oxigênio no sangue (BOLD) para os paradigmas funcionais.

Análise de dados: A análise de dados de fMRI foram feitas usando um modelo linear geral (GLM) em FSL com as imagens funcionais no sentido de mapear regiões motoras e regiões relacionadas com a aquisição e recordação da memória. A ferramenta FSL MELODIC foi utilizada para fazer a análise probabilística de componentes independentes (ICA) para dados motores e de memória, e também a ferramenta FSL FEAT foi utilizada para pré-processamento e análise de dados.

Eliminação de ruído usando ICA: Artefactos associados ao movimento podem influenciar a compreensão de redes funcionais e a sua relação com variáveis de diferenças individuais e de grupo. Portanto, foram usadas técnicas que visam a remoção de artefactos, de modo a reduzir múltiplas flutuações de ruído. Para eliminar o ruído, componentes ICA derivados dos dados da memória e o comando fsl_regfilt foram utilizados.

Análise de região de interesse (ROI) envolvendo aperto de mãos: Os dados de aperto de mãos provenientes do FEAT foram usados para gerar uma máscara binária com SPM ImCalc, criada usando a ferramenta SPM em ambiente MATLAB. A máscara de aperto de mãos e as imagens de memória 3D foram submetidas a um algoritmo para realizar o cálculo de uma imagem de máscara binária com pixels dentro do ROI cujo objetivo foi realizar uma análise de agrupamento temporal (TCA) para inferir a estimativa das médias das séries temporais. Após a realização dos gráficos do TCA foram produzidos os gráficos das séries temporais do estímulo de memória.

Cursos de Tempo de Referência (RTCs): Com a série temporal da memória, foi definido um mapa bidimensional, onde o limiar corresponde ao momento em que se considera que um evento ocorre. Estes foram denominados cursos de tempo de referência (RTCs) que são colunas que representam

histogramas individuais de aumentos significativos para os vóxeis cujo aumento máximo de sinal ocorreu num ponto de tempo exato. Os RTCs devem indicar se as respostas fornecidas pelos pacientes estão corretas ou não. Para realizar isso, foi feita uma comparação entre as respostas verdadeira/falsa do paradigma espectável da função de resposta hemodinâmica (HRF) de memória e os dados HRF do paciente para selecionar as respostas corretas e incorretas.

Análise quantitativa dos dados: Foi realizada uma análise quantitativa, para auxiliar na interpretação fisiológica. Com os RTCs, foram encontradas respostas corretas e incorretas fornecidas pelos pacientes, levando-se em consideração também as regiões anatómicas que denotaram maior ativação. Para isso, foi utilizado o xjView, que forneceu a informação dos dados a nível anatómico. Tendo informações sobre as regiões anatómicas, os dados foram comparados entre os pacientes de modo a entender quais eram os padrões entre aqueles que tiveram melhor desempenho e pior desempenho sendo tiradas conclusões dessas análises

Com base na análise quantitativa dos dados, pôde-se observar que metade dos pacientes forneceu a resposta correta, enquanto a outra metade não. Observou-se também que nenhum paciente acertou todas as questões, tendo acertado no máximo 75% - 99% das questões.

Encontrámos informações relevantes na tarefa relacionada com respostas motoras. Neste paradigma de memória com tarefas motoras, as regiões motoras foram ativadas conforme o esperado, tais como a área motora suplementar, giro pré-central, giro pós-central, córtex somatossensorial primário e córtex motor primário. A inclusão de uma resposta motora resultou numa sobreposição de respostas de memória com respostas motoras, o que, de acordo com Kinder and Buss 2020, melhora a aquisição da memória. Além das regiões motoras, foram encontradas ativações no córtex auditivo, que processa as informações auditivas; lobo frontal, que é importante para o movimento voluntário; mesencéfalo, que desempenha funções importantes nos movimentos motores e no processamento auditivo e ativação do hipocampo também foi observada. Além disso, também foram encontradas regiões relacionadas à codificação da memória, como giro temporal superior, cúlmen, giro pré-central, cerebelo e o declive.

A partir dos resultados e da discussão, podemos concluir que o paradigma da memória suportado por uma resposta motora leva a resultados claros e robustos de acordo com as expectativas.

Embora os resultados deste estudo não sejam afetados, existem algumas limitações na nossa metodologia que devem ser consideradas. O tamanho da nossa amostra de 12 pacientes ainda é relativamente pequeno num contexto de um estudo piloto de uma amostra de pacientes relativamente homogénea a nível clínico. O fato de não termos um grupo de controlo pode ser visto como outra limitação deste estudo. Para um estudo futuro, também seria benéfico realizar fMRI durante a aquisição da memória. Para realizar um estudo comparativo com melhores resultados, pode-se continuar com a execução do mesmo paradigma de memória, mas utilizar outros métodos de resposta aos estímulos, nomeadamente os botões como resposta, de forma a comparar os resultados de forma mais direta.

Ainda há um longo caminho a percorrer, ao nível do conhecimento, do impacto da TLE na memória, como dos paradigmas que devem ser considerados, visto que não existe um protocolo de fMRI de memória "padrão" devido à variabilidade dos parâmetros a serem considerados.

Palavras-chave
Epilepsia; memória; epilepsia do lobo temporal; ressonância magnética funcional; paradigma

Abstract

Temporal Lobe Epilepsy (TLE) can cause memory impairment, being estimated to account for approximately 40% of all epilepsies in adults. For the 76,8% of cases that do not respond farmacologically, neurosurgery is the treatment of choice. Nonetheless, 30% of patients show memory decline after intervention, rendering memory functional mapping key to prevent such outcomes. Thus, this study aimed to assess the functional network associated with memory in patients with TLE.

To test the hypothesis that it is possible to achieve clinical levels of accuracy using the hand grasping and face-name memory paradigm designed in this study, fMRI data were collected and analysed from 12 patients diagnosed with TLE. The analysis was done using FSL tools, MATLAB, SPM, and xjView, whilst artefact removal techniques were used as well, followed by hand-grasping region-of-interest analysis to indicate whether the answers given by the patients during paradigm execution were correct.

It was observed that half of the patients gave the correct answers, while the other half did not. It was also observed that none of the patients answered all the questions correctly, having answered correctly at most 75% - 99% of the questions.

In this memory paradigm with motor tasks, motor regions were activated as expected, such as the supplementary motor area, precentral gyrus, postcentral gyrus, primary somatosensory cortex, and primary motor cortex. Additionally, regions related to memory encoding were also found, such as the temporal lobe and frontal lobe superior temporal gyrus, culmen, precentral gyrus, cerebelum and the declive. Some regions such as hippocampus, fusiform and insula also match what was found in other studies.

From the results and the discussion, we can conclude that the memory paradigm supported by a motor response leads to robust results in agreement with expectations.

Keywords
Epilepsy; memory; temporal lobe epilepsy; functional magnetic resonance imaging; paradigm

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

%RC	Percentage of Correct Answers
%TRC	Total Percentage of Correct Answers
BOLD	Blood Oxygenation Level Dependent
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CMRO2	Cerebral Oxygen Metabolic Rate
CNS	Central Nervous System
CT	Computed Tomography
EEG	Electroencephalography
FEAT	fMRI Expert Analysis Tool
fMRI	Functional Magnetic Resonance Imaging
FOV	Field-of-View
FS	Febrile Seizures
FSL	FMRIB Software Library
GLM	General Linear Model
GTAV	Audio Visual Technologies Group
GTCS	Generalised Tonic-Clonic Seizure
GUI	Graphical User Interface
HGS	High Global Score
HRF	Hemodynamic Response Function
HS	Hippocampal Sclerosis
IBEB	Institute of Biophysics and Biomedical Engineering
ICA	Independent Component Analysis
LGS	Low Global Score
MATLAB	MATrix LABoratory
MELODIC	Multivariate Exploratory Linear Optimised Decomposition into Independent Components
MGS	Medium Global Score
MPRAGE	Magnetization Prepared RApid Gradient Echo
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MTL	Mesial Temporal Lobe
MTLE	Mesial Temporal Lobe Epilepsy
MTS	Mesial Temporal Sclerosis
NTE	Neocortical Temporal Epilepsy

PCA	Number of Patient's Correct Answers
PIC	Number of Patient's Incorrect Answers
RC	Correct Answers
RF	Radio Frequency
ROI	Region-of-Interest
RTC	Reference Time Courses
SPM	Statistical Parametric Mapping
TCA	Temporal Clustering Analysis
TE	Echo Time
TLE	Temporal Lobe Epilepsy
TR	Repetition Time
TRC	Total Correct Answer

Chapter 1
Introduction

This project was developed as part of a collaboration between the Institute of Biophysics and Biomedical Engineering (IBEB) and the Hospital de São José.

IBEB is a research unit of the Faculty of Science of the University of Lisbon whose mission is to improve scientific knowledge and training on the physical and physiological aspects underlying human oncology and neuroscience, in order to apply them for the benefit of society.

1.1. Context and Motivation

Memory is the process by which information is encoded, stored, and retrieved over time. A key function of memory is that it enables us to distinguish between stimuli that have been previously encountered and new stimuli [1].

We will see that memory can be conceptualised in terms of Types, Stages, and Processes. We will look at the two types of memory, (i) explicit memory and (ii) implicit memory. And then the three main stages of memory, (i) sensory memory, (ii) short-term memory and (iii) long-term memory. Finally, we will focus on the three main processes of human memory: (i) encoding, (ii) storage and (iii) retrieval.

Our brain is a network. It consists of spatially distributed, but functionally linked regions that continuously share information with each other. In order for this to happen, functional connectivity, which is the temporal dependency of neuronal activation patterns of anatomically-separated brain regions, must take place as flawlessly as possible [2]. But sometimes, changes in the structure of the brain, brain infection or disease, stroke, oxygen deficiency or genes causes neurological disorders that may jeopardise the normal functioning of the brain [3].

Epilepsy is broadly defined by a state of recurrent spontaneous seizures, which arise when the balance between excitation and inhibition is disrupted [4], [5]. Medication is usually used to treat epilepsy, but in some cases, neurosurgery is performed. For this intervention, it is necessary to identify the epileptogenic focus or zone, i.e., the area of the cerebral cortex responsible for triggering epileptic seizures.

Epilepsy is one of the most common serious brain disorders, affecting about 50 million people worldwide. Epilepsy accounts for 1% of the global burden of disease, whilst 80% of the burden of epilepsy occurs in developing countries, where in some areas 80-90% of people with epilepsy receive no treatment at all [6].

Temporal Lobe Epilepsy (TLE) is a chronic neurological disorder characterised by recurrent epileptic seizures originating in the temporal lobe. Patients with TLE may have memory deficits related to Mesial Temporal Lobe dysfunction. It is the most common form of focal epilepsy. About 6 out of 10 people with focal epilepsy have TLE. Moreover, TLE involves seizures that typically originate in the hippocampus [7].

Declarative memories, episodes, and facts you can consciously recall are stored and retrieved in the hippocampus but are also stored throughout the brain. Each element of a memory, the sight, sound, word, or emotion that makes it up, is encoded in the same part of the brain that originally created that fragment. However, previous studies have shown that individuals with TLE have significant material specific episodic memory impairments with greater verbal and visual memory deficits [8], [9]. It is more and more undisputed that memory is a "network function", while at the same time it is known that the mesial temporal structures play a critical role in it.

Surgery remains an essential option for the treatment of medically intractable TLE. The main goal of epilepsy surgery is complete resection of the epileptogenic focus with little consequence on eloquence.

In this work, functional magnetic resonance imaging (fMRI) was used to acquire images to analyse cognitive function since it is a non-invasive method that has demonstrated to be powerful in the investigation of brain activity and networks. During an fMRI study, images of the brain are acquired along with the performance of some tasks set by the paradigm created. fMRI is an indirect method of measuring brain activity since it is not directly based on the electrical activity of neurons. Instead, it measures how the circulatory system responds to the increasing energy requirements of the activated brain cells. In more general terms it can be said that the purpose of fMRI analysis is to detect on a robust, sensitive and valuable way, brain regions that show an increase in blood oxygenation level dependent (BOLD) signal intensity at the times when stimulation was applied [10].

The most commonly used method in fMRI is based on BOLD contrast to study local changes in deoxyhaemoglobin concentration in the brain [11]. [13]

The main evoked haemodynamic response to a neural event is usually referred to as the haemodynamic response function (HRF). It is worth noticing that fMRI has some limitations in terms of temporal resolution, which determines our ability to separate brain events in time. For this reason, electroencephalography (EEG), which is a technique with much better temporal resolution, is currently being studied as a complementary element to fMRI studies. Spatial resolution, which determines our ability to distinguish changes in an image across locations, appears to be the strength of fMRI.

Assuming a linear relationship between stimulation and BOLD response, the continuous signal produced by a specific time course of stimulation can be predicted within the General Linear Model (GLM) [12]. A general linear modelling sets up a model and fits it to the data. If the model is derived from the timing of the stimulation that was applied to the patient in the Magnetic resonance imaging (MRI) scanner, then a good fit between the model and the data means that the data were probably caused by the stimulation [10].

Task-based functional magnetic resonance imaging is an fMRI technique that can be used to detect changes in the BOLD haemodynamic response to neural activity in response to specific events [12].

Any clinical application of fMRI involves a paradigm, a defined functional measurement, and a task that is likely to activate the cortical area under investigation. A paradigm typically consists of control and activation conditions, usually triggered by an external stimulus. Finally, the ideal memory fMRI paradigm, once designed, needs to be reproducible and validated at the clinical level.

Therefore, what motivate us to develop this project is the desire to deepen our understanding of the functional network associated with memory in patients with TLE. Understanding the memory network in TLE patients through fMRI can provide crucial insights into the disease's underlying mechanisms and aid in developing better treatment approaches.

1.2. Problem Statement and Objectives

TLE is the most frequent in adults, accounting for about 40% of all epilepsies [13]. One of the main characteristics of TLE is its resistance to drug treatment in a significant proportion of patients. It is estimated that in about 76.8% of cases, conventional drugs fail to effectively control epileptic seizures, making the patient refractory to pharmacological treatment.

Due to drug resistance, surgery becomes an important option for the treatment of TLE. Surgical intervention aims at complete resection of the epileptogenic focus in the temporal lobe, seeking to reduce or eliminate epileptic seizures and improve the patient's quality of life.

However, even with surgical treatment, not all patients achieve freedom from epileptic seizures. Studies show that only about 66% of patients undergoing surgery achieve seizure freedom after the intervention. In addition, more than 30% of patients undergoing surgery may experience memory decline after the procedure, which poses an additional challenge in the management of TLE [14].

Given the complexity of TLE and the importance of memory in patients' quality of life, research has been conducted to better understand the functioning of the neural network associated with memory in patients with this condition. In this context, the use of fMRI has proven to be a valuable tool, allowing the analysis of memory-related brain activity and its functional connectivity in patients with TLE.

The use of adapted memory paradigms, such as this one with hand grasping, may contribute to collect relevant information from patients during the study, enhancing the understanding of memory deficits associated with TLE.

Additionally, this study also aims to assess the functional network associated with memory in patients with TLE. And also determine the memory network in individuals with temporal lobe epilepsy through a regression of inference responses provided by the patients themselves.

For this end, (i) a design of a suitable functional paradigm will be made, and (ii) the data acquisition and (iii) data analysis will be performed using the GLM and Independent Component

Analysis (ICA). Based on the observed network (iv) an evaluation of the functional network interface will be made, and finally (v) the interpretation and discussion of the obtained results will be presented.

1.3. Main Contributions

Conventional memory paradigms require complex and/or costly instrumentation, which prevents their wider adoption. Therefore, a memory paradigm involving hand grasping was adapted here to seamlessly collect patient feedback. Connectivity is the main problem of epilepsy, since its defining element is the occurrence of seizures. To reduce the number of seizures, we need to understand how one of the most common drug-resistant epilepsies, TLE, works [15], [16]. Since TLE is defined by cell loss and gliosis in the hippocampus, entorhinal cortex and amygdala, which are involved in memory encoding, storage and retrieval, understanding and determining the memory network in TLE patients through fMRI is crucial [8].

The hypothesis to be tested is to understand whether it is possible to achieve the same level of accuracy using the hand grasping and memory paradigm carried out in this study as it is when using other paradigms, such as buttons as a response to stimuli. And from the results of this study, we can see if we can conclude that the paradigm used is valid compared to what is reported in the literature. If it is valid, it can be an asset for preoperative assessment in hospitals where there are no other ways to do this assessment.

1.4. Dissertation Organization

For the state-of-the-art research, a systematic strategy of searching for information in different databases was adopted. The search was conducted in databases such as PubMed, Frontiers, ScienceDirect and other academic sources, covering the period from 2000 to 2022. The following keywords were used: epilepsy; memory; temporal lobe epilepsy; functional magnetic resonance imaging; paradigm. In order to ensure the selection of relevant studies, inclusion criteria were established, which encompassed memory studies in epilepsy, specific diagnosis of TLE, results obtained with different paradigms, data availability, in order to be able to make a comparative analysis. This research approach allowed us to obtain a comprehensive view of the current state of knowledge on the topic, providing a solid basis for the development of this study.

This thesis is divided into 5 main chapters, namely (1) Introduction, (2) Background, (3) Methodology, (4) Results and Discussion, and (5) Conclusions.

Chapter 1 gives a brief introduction to the issues addressed in the thesis, refers to the objective, establishes a theoretical framework and finally states the hypothesis to be tested.

Chapter 2 provides the reader with a background on epilepsy, TLE, memory, fMRI and the paradigm design, reviewing academic literature.

Chapter 3 provides an overview of the research strategy and methodology used to ensure understanding of how the findings were collected and how the research was approached.

Chapter 4 presents and discusses the findings of the study by highlighting, quantifying and comparing the findings with other studies.

Chapter 5 concludes the thesis by reviewing the original question/hypothesis and the aim of the research and weighing up the limitations and next steps to be taken.

Chapter 2
Background

2.1. Memory

The brain is the most complex organ of the human body, and that makes it the least understood part of the entire body. It is made up of millions of neurons that communicate with each other using specialised chemicals called neurotransmitters. There are so many things we know about the brain, but there is so much more we do not know. The paradox of memory is one of those topics that we have deepened our knowledge of over time. And the study of memory has such relevance, since memory is what makes us who we are.

Memory is the process by which information is encoded, stored and retrieved over time. A key function of memory is that it enables us to distinguish between stimuli that have been before encountered and those that are new [1].

Until about a decade ago, most researchers thought that forgetting was a passive process. A process whereby memories that have not been used decay over time. But they are beginning to realise that remembering and forgetting are the two crucial components of memory [17].

Despite the obvious benefits of memory, it can also fail us. According to the American Psychological Association, memory has seven sins: **Transience** - the decreasing accessibility of memory over time, it fades with time; **Absent-mindedness** - we do not remember what we do not pay attention to; **Blocking** - temporary inaccessibility of stored information, since our memories can be temporarily blocked; **Suggestibility** - incorporation of misinformation into memory due to leading questions; **Bias** - retrospective distortions produced by current knowledge and beliefs; **Persistence** - unwanted recollections that people can't forget; **Misattribution** - attribution of memories to incorrect sources or believing that you have seen or heard something you haven't. The first three are "sins of omission" that involve forgetting, and the second four are "sins of commission" that involve distorted or unwanted recollections.

In this section we will see that memory can be conceptualised in terms of Types, Stages, and Processes. We will look at the two types of memory, (i) explicit memory and (ii) implicit memory; and then the three main stages of memory, (i) sensory memory, (ii) short-term memory and (iii) long-term memory. At last, we will focus on the three main processes involved in human memory, (i) encoding, (ii) storage, and (iii) retrieval. Table 2.1 resumes the conceptualisations.

Table 2.1 Memory in Terms of Types, Stages, and Processes [18].

Types	• Explicit (Declarative) memory • Implicit (Non-declarative) memory
Stages	• Sensory memory • Short-term (Working) memory • Long-term memory
Processes	• Encoding • Storage • Retrieval

2.1.1. Memory Types

Memory function is critical to daily life and includes a variety of specific abilities that, at their core, enable information to be stored and retrieved over variable periods of time, ranging from seconds to days to years. Researchers and theorists have extended the basic multi-store model in many ways. Perhaps the most fundamental of these distinctions is the:

(a) Explicit (declarative) memory and
(b) Implicit (non-declarative) memory

As mentioned earlier, there are two types of long-term memory, and from Figure 2.1 we can better understand what the subdivisions are.

The domain of explicit memory requires conscious awareness and is therefore often referred to as declarative memory. The domain of implicit memory includes several forms of learning that occur during the performance of various tasks and are therefore also referred to as non-declarative memory. They usually manifest themselves in enhanced or speeded behavioural performance or in a change in behavioural decisions or values.

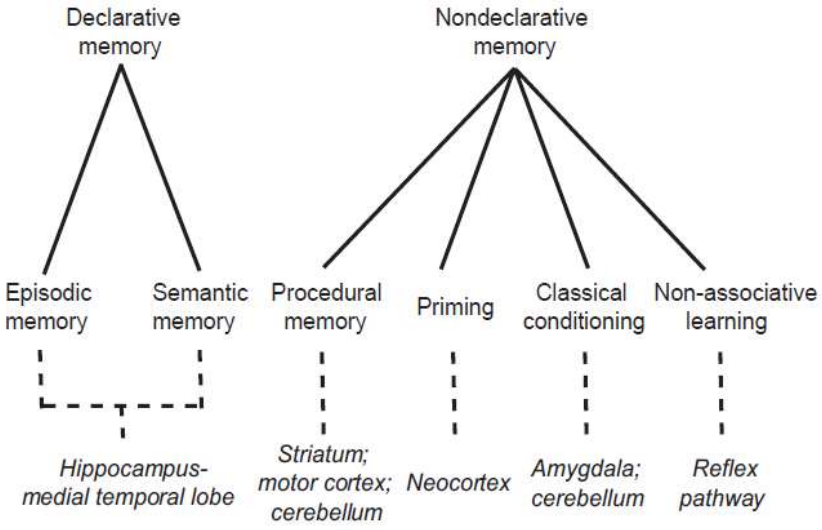

Figure 2.1: Taxonomy of memory systems [19]

2.1.1.1. Explicit (or declarative) memory

Explicit memory, often referred to as declarative memory, can further be divided into:

(i) Episodic memory and

(ii) Semantic memory.

Overall, explicit memory continues to develop over the years, including rapid changes in the first two years of life until the age of 60, when it gradually declines [20].

Episodic memory refers to the ability to consciously recall personal event information and spatiotemporal relations from previous experiences [21]. These are memories that relate to an individual's own unique experience and include the details of "when and where" an event occurred. Most memory tests assess episodic memory and usually involve a free recall (retrieval), cued recall, and recognition trial and rely on an individual's ability to recollect the material to which he or she was previously exposed [22]. In general, episodic memory occurs through extensive connections between the neocortex (the prefrontal cortex, the amygdala, the anterior temporal cortex) and the parahippocampal regions and the hippocampus (which is considered to be the most critical structure in forming episodic memory) [20].

Semantic memory consists of stored information about features and attributes that define concepts. It is a person's knowledge of the world and includes memory of the meanings of words (vocabulary), facts and concepts and, unlike episodic memory, is not context dependent. The visual encoding of a scene, in order to remember and recognise it later (i.e., visual memory encoding), engages both episodic and semantic memory, and an efficient retrieval system is required for later recall [21][22].

2.1.1.2. Implicit (or nondeclarative) memory

Implicit memories are sometimes called non-declarative because a person is unable to verbally declare these memories. Implicit memories are non-conscious, and often involve memories for specific

step-by-step procedures or of certain feelings/emotions. Implicit memory refers to a way in which the influence of recent experiences may be expressed in subsequent task performance unintentionally and without conscious recollection of a learning episode of those experiences [23], [24].

Implicit memory encompasses a wide range of phenomena, including procedural and motor memory, habit learning, classical conditioning, and emotional / non-associative memory [23], [25].

Priming

This type of implicit memory is known as priming, or changes in behaviour as a result of experiences that have happened frequently or recently [18]. There are three types of priming that have been most often studied: visual word priming; visual object priming; and auditory word priming [23]. Priming refers both to the activation of knowledge and to the influence of that activation on behavior [18].

Procedural memory

Procedural memory refers to our often-unexplainable knowledge of how to do things. Such skills are stored in brain areas that lie beneath the cortex. They can be recalled to mind, but usually remain unconscious [26]. Procedural memory is a category of long-term memory that involves recollections to which a person has no direct conscious awareness. It can only be demonstrated indirectly through some type of motor action, for example, how to swim or ride a bicycle. Procedural memory involves the functions of the dorsolateral striatum, the cerebellum, and the limbic system.

Classical conditioning

Classical conditioning is one of the most fundamental ways of learning and has been important in theories of both experimental psychology and clinical psychology [27]. It is learning through association and was discovered by Pavlov, a Russian physiologist. In simple terms, two stimuli are linked together to produce a new learned response in a person. In classical conditioning, we learn, often without effort or awareness, to associate neutral stimuli, such as a sound or a light, with another stimulus, such as food, which creates a naturally occurring response, such as enjoyment or salivation. The memory for the association is demonstrated when the conditioned stimulus (the sound) begins to create the same response as the unconditioned stimulus (the food) did before the learning [18].

Non-associative learning

Non-associative learning occurs in response to a single stimulus, without reinforcement and it involves sensitisation, habituation and imprinting.

2.1.2. Memory Stages

According to the Stage Model, there are three memory systems:

(i) Sensory memory,
(ii) Short-term memory,
(iii) Long-term memory

Each of these systems have different features and perform different functions with respect to the sensory inputs. As shown in Figure 2.2. We can think about memory in terms of stages that describe the length of time that information remains available to us. According to this approach, information

begins in sensory memory, moves to short-term memory, and eventually moves to long-term memory. But not all information makes it through all three stages.

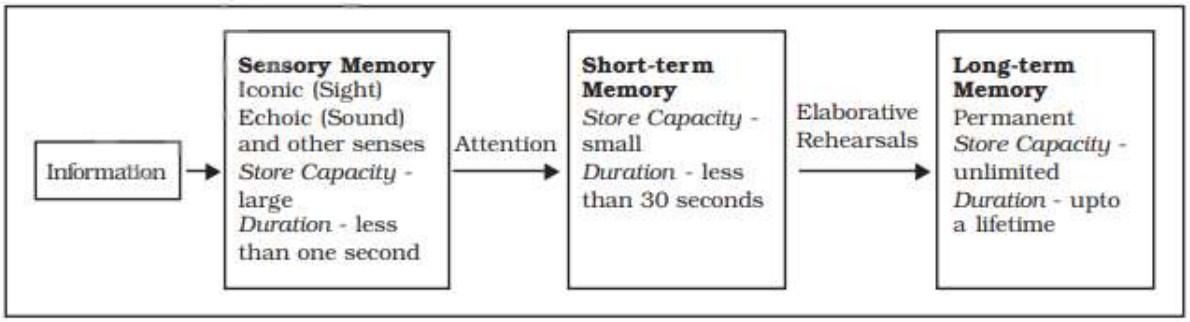

Figure 2.2 The Stage Model of Memory. Memory can be characterised in terms of stages — the length of time that information remains available to us [28]

2.1.2.1. Sensory memory

Sensory memory takes information from the environment through the human senses (proprioception, sight, hearing, taste, touch and smell). It is recollection of perceptual types of how a stimulus looks, feels, sounds, etc. [29]. Sensory memory can take a lot of information, but this information is stored for only a very short time. It is a memory system that registers information from each of the senses with reasonable accuracy.

2.1.2.2. Short-term memory

Short-term memory (Working memory = structured short-term memory) is a declarative memory, it's what you are conscious of or what you are thinking about at any given moment. It involves the short-term maintenance of information in mind, and often the manipulation of that information for the purpose of achieving an immediate goal. Short-term memory involves medial temporal lobes structures, like the hippocampus and the medial diencephalic structures, as well as a few cortical areas. The hippocampus is an "old" cortical area involved in multiple aspects of memory. The Left hippocampus is more involved in the learning and memory of facts, episodes, and words. The Right hippocampus is more involved in spatial memory. The hippocampus compares the present experience with past experience; and the processing through the hippocampus is necessary for learning and for memory consolidation to occur.

In 1974, Baddeley and Hitch developed an alternative model of short-term memory which they termed as working memory [30]. Working memory is the platform where we hold and manipulate thoughts and is foundational to the organisation of goal-directed behaviour, it is the fundamental function by which we break free from reflexive input-output reactions to gain control over our own thoughts [31]. Working memory is important for comprehending long written or spoken sentences, performing calculations, and holding in mind a string of new information or a series of movements. Performing multiple simultaneous tasks also requires working memory.

2.1.2.3. Long-term memory

Long-term memory is where we hold all our memories. One goal of learning is to get information into long-term memory so we can use it later when we need it. This is a (declarative memory) episodic memory and semantic memory [32], [33]. Long-term memory involves widespread areas of the cortex. So, information in there can "fade", but widespread loss is rare. Implicit memory and explicit memory represent the distinct neural processes and the different states of awareness of our long-term memory.

2.1.3. Memory Processes

As mentioned above, there are three main processes involved in human memory: Encoding, Storing and Retrieving. It is important to understand that they are central to long-term memory.

2.1.3.1. Memory Encoding

The first process that memory puts in operation is known as encoding, comprising receiving, processing and combining the received information. There are three main ways in which information can be encoded,

(i) Visual (picture),
(ii) Acoustic (sound) and
(iii) Semantic (meaning).

2.1.3.2. Memory Storage

The second process is the storage and is characterised for creation of a permanent record of the encoded information. This concerns the nature of memory stores, i.e.

(i) where the information is stored,
(ii) how long the memory lasts for (duration),
(iii) how much can be stored at any time (capacity) and
(iv) what kind of information is held.

The way we store information affects the way we retrieve it. As long as information is stored, it is permanently transformed, reorganised, and included in new links even if the subject is not fully aware of the process.

2.1.3.3. Memory Retrieval

The last process is retrieval in which the recall of the stored information occurs in response to some incitement for use in a process or activity. Memory retrieval occurs by recognition or by recall:

(i) Recognition is an experienced or encountered event association and involves an information comparison process with memory. e.g., recognising a known face, true/false, or multiple-choice questions.
(ii) Recall involves remembering a fact, event, or object and requires the direct retrieval of information from memory. e.g., remembering the name of a recognised person.

2.1.4. Memory Methods

Psychologists like to make the distinction between two types of memory retrieval: **recognition** versus **recall**. Human memory processes can be classified as the ability of the mind to understand, retain, and successfully recall information. The role of retention is to store encoded events and information, and the role of recall is to re-access the retained events and information in the mind in response to external stimuli [34]. Recognition refers to our ability to "recognise" an event or piece of information as being familiar, while recall designates the retrieval of related details from memory. The big difference between recognition and recall is the number of cues that can help the memory retrieval; recall involves fewer cues than recognition. [35].

Although memory is achieved in multiple phases, recall is the only way to measure memory performance. There are many factors that affect retention and recall performance, such as attention, rehearsal, sleep, testing, mnemonics, exercise and nutrition, and reward [34].

2.1.5. Memory Network

Memory encoding involves a network of regions including the cerebral cortex of the frontal, parietal, and temporal lobes; the hippocampus; the amygdala; and the diencephalon as shown in Figure 2.3.

Cerebral Cortex

The outer covering of grey matter on the hemispheres is the cerebral cortex. It is a thin layer of tissue and covers the outer portion of cerebrum up to 5 mm [34].

Hippocampus

The hippocampus is strung along the upper edge of the parahippocampal gyrus. The hippocampus interlocks with another ridge, known as the dentate gyrus—together the two form the hippocampal–dentate complex. The main functions of the hippocampus include spatial awareness, and memory formation and recall. In particular, the hippocampus helps select transient information for memorising and then pass it through to longer-term memory areas. Damage to it can prevent a person from forming new memories, even though memories from before the damage are intact [26].

Amygdala

The amygdala is in the deep anterior inferior medial temporal lobe near the hippocampus and holds 13 nuclei, each of which has other subsystems. The amygdala itself is not a storage place for memory but influences the consolidation and acquiring of memories in various learning situations in the brain, such as interactions with the hippocampus in emotional memory, involvement in memory storage in other brain systems [34].

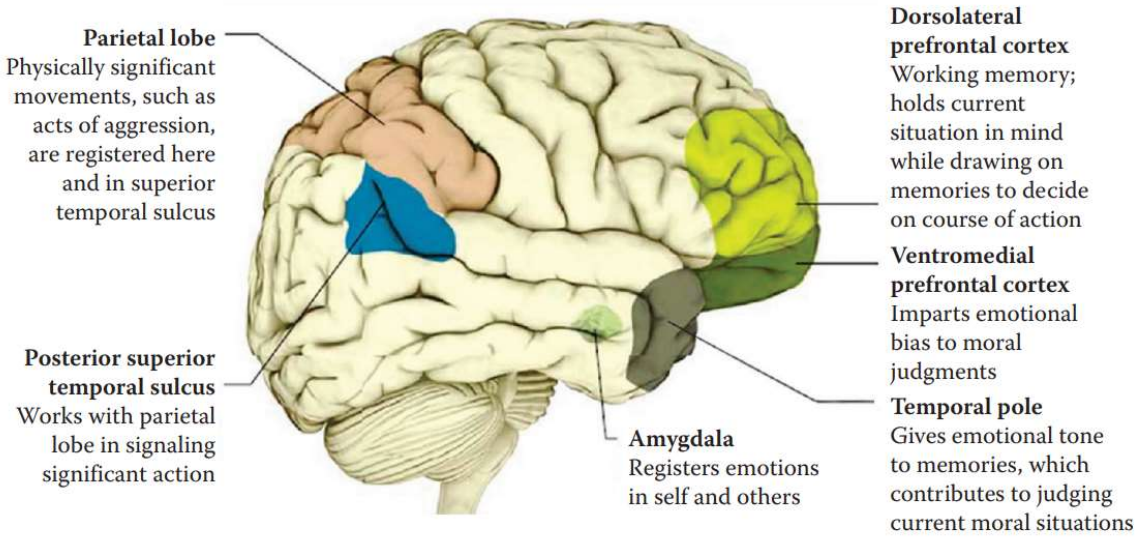

Figure 2.3 Brain regions associated with memory functions [26]

The regions specific to word encoding, according to Sidhu et al. 2013 [36], shows that healthy subjects have activation in regions as the left prefrontal cortex and left hippocampus, and from that, subsequent verbal memory effects are displayed within the left parahippocampal gyrus, left orbitofrontal cortex and fusiform gyrus. According to the same study, during face encoding subjects show right lateralised prefrontal cortex and bilateral hippocampal activations, and subsequent visual memory effects within right amygdala, hippocampus, fusiform gyrus and orbitofrontal cortex. The orbitofrontal cortex is critical to subsequent memory formation.

Taking into account the methodology applied in this work, it becomes important to address another type of memory and its neural networks: the procedural memory which is the memory related to the performance of particular types of actions. This type of memory resides below the level of conscious awareness, being automatically retrieved and utilised for the execution of the integrated procedures involved in both cognitive and motor skills. This type of memory is created through repeated activities which allow the neural system to work in order to automatically produce the activity. In this work the subjects were indicated that they should give motor responses, hand movements, to indicate the answers as correct or incorrect, and since that type of movement is considered to be an automatic activity, it was taken into consideration for the analysis to be performed in the future in this work. According to the literature, procedural memories, unlike the declarative memory, do not appear to involve the hippocampus at all. The neuroanatomy of procedural memory is not very clear but studies suggest that the encoding and storage is made by cerebellum, basal ganglia (putamen, caudate nucleus) and the motor cortex, all of which are involved in motor control [37]–[39].

2.2. Epilepsy

Epilepsy is one of the most common serious disorders of the brain, affecting about 50 million people worldwide. Epilepsy accounts for 1% of the global burden of disease, whilst 80% of the burden of epilepsy is in the developing world, where in some areas 80–90% of people with epilepsy receive no treatment at all [6].

The word “epilepsy” comes from the Greek and means to be taken, seized or attacked. Epilepsy is a multifaceted disease with various clinical characteristics. It is defined by a state of recurrent, spontaneous seizures, which arise when the balance between excitation and inhibition is disrupted [4], [5]. It can be brought by a change in the structure of the brain, brain infection or disease, stroke, lack of oxygen or gene expression. Although in 2014 this definition was updated to a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome [3].

Epileptic seizures reflect abnormal neuronal synchronisation as much as alterations in excitability; and synchronisation can only be studied at the level of neuronal networks. Seizure then is a period of abnormal, synchronous excitation of a neuronal population, arising when there is a disruption of mechanisms that normally create a balance between excitation and inhibition. Seizures typically last seconds or minutes and the clinical manifestations vary, wherein some seizures may not involve muscular contractions (convulsions) at all. It is important to clarify that one seizure that occurs in an individual does not automatically classify him/her as an epileptic.

The development of epilepsy (**epileptogenesis**), and the generation of spontaneous seizures (**ictogenesis**), are emergent properties of aberrant functional and structural connections between individual neurons to produce hypersynchrony, and large brain areas to permit propagation and the manifestation of clinical signs and symptoms. Epilepsy can then ultimately be regarded as a disorder of neuronal connections [4], [5]. That being said, to treat epilepsy usually medication is used, but in some cases neurosurgery is necessary. In order to make this procedure, it is necessary to identify the epileptogenic focus, which is the area of the cerebral cortex responsible for causing epileptic seizures. So, the removal of this region has a high probability of leave the patient free of crises.

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years [3].

2.2.1. Causes of Epilepsy

In about 70% of people with epilepsy, the cause is not known. In the remaining 30%, the most common causes are head trauma, brain tumour, genetic, and infection of brain. Epilepsy may develop after a particular identifiable cause, in which case it is called **symptomatic epilepsy**, or it may develop without any identifiable cause, and then it is called **idiopathic epilepsy**. When the cause is hidden or occult, with no defined electro-clinical characteristics it is called **cryptogenic epilepsy**.

In Figure 2.4 we can see different causes of epilepsy according to their relative frequency and age. We can see that epilepsies can start at any age. For instance, birth trauma may result in permanent changes of brain tissue, i.e., scar tissue. In fact, any area with abnormal brain tissue, e.g. calcifications, scars, or vascular abnormalities, may act as a focus from where abnormal activity of the neurons takes place causing "symptomatic epilepsy" [40].

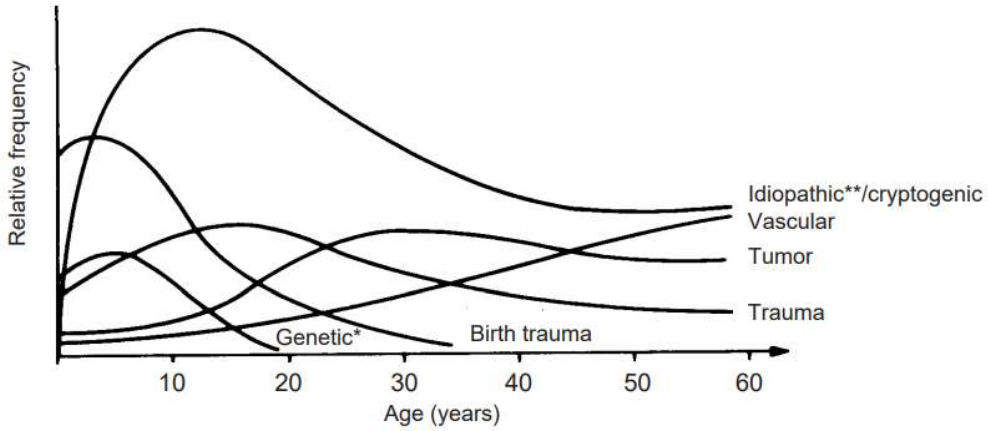

Figure 2.4 Approximate frequency of different causes of epilepsy, developing at different years [40]. * Genetic brain disorders with epilepsy. **Idiopathic = genetic epilepsy without other disorders = epilepsy *sui generis*.

The symptomatic epilepsies are considered to be the consequence of a known or suspected disorder of the central nervous system. Most of the localisation-related epilepsies are symptomatic, so with intensive investigation methods, a lesion or focus can be found. The focus might be in the frontal, temporal, parietal or occipital lobes of the brain as we can see in Table 2.2 or in the motor cortex. The temporal lobe epilepsy will be the one we will be more focused on.

Table 2.2 Epilepsy related to anatomic localisation. Different types of epilepsy and the indication of seizure type, symptoms and special features related to them. **GTCS**: Generalised tonic-clonic seizure [40]

Frontal lobe epilepsy	
Seizure type	simple partial and complex partial; often rapid secondary generalisation; *status epilepticus* is frequent
Symptoms	versive movements of the head; prominent motor manifestations, which are tonic or postural; especially in the legs; complex gestural automatisms at onset
Special features	short seizures, several times a day and often during sleep despite impairment of consciousness, often minimal or no postictal confusion; sometimes mistaken for psychogenic seizures
Temporal lobe epilepsy	
Seizure type	complex partial, simple partial, and sometimes with secondary generalisation
Symptoms	epigastric rising sensation and hallucinations; motor arrest followed by oroalimentary automatisms; followed by other automatisms
Special features	there is frequently a history of febrile convulsions; a family history of convulsions is common; memory deficits onset is frequently in childhood or young adulthood; seizures occur in clusters at intervals or randomly postictal confusion and gradual recovery
Parietal lobe epilepsy	
Seizure type	simple partial ± secondary GTCS
Symptoms	sensory, like tingling or a feeling of electricity numbness, sometimes painful sensations, usually in hand, arm or face; may spread in a Jacksonian manner
Occipital lobe epilepsy	
Seizure type	simple partial ± secondary GTCS
Symptoms	fleeting visual manifestations like sparks, flashes and phoshenes; perceptive illusions

2.2.2. Temporal Lobe Epilepsy (TLE)

TLE is a chronic neurological condition characterised by recurrent, epileptic seizures originated in the temporal lobe. Patients with TLE may have memory deficits related to Mesial Temporal Lobe dysfunction. It is the most common form of focal epilepsy with about 6 out of 10 people with focal epilepsy having TLE. Temporal lobes are the most epileptogenic regions of the human brain. Hippocampal Sclerosis (HS) is the commonest cause of TLE, and it is estimated that it represents about 40% of all epilepsies in adult people [7].

The most important cognitive comorbidity in TLE is impairment in episodic memory. The hippocampus plays an important role in the generation and propagation of temporal lobe seizures and is also a critical structure for long-term memory, including episodic memory. It follows that impairments in memory and learning are commonly seen in people with TLE [41].

The TLE involves seizures that typically originate in the hippocampus. It is the most common drug-resistant epilepsies in adults, being usually related to Mesial Temporal Sclerosis (MTS), as its surgical removal results in clinical meaningful improvement in about 70% of patients [15], [16]. Therefore, one can affirm that the most common cause of this disorder is the MTS which affects usually structures located in the medial and lateral temporal cortex, in particular the hippocampus, the parahippocampal gyrus and the amygdala [42].

2.2.2.1. Types of TLE

Nowadays two syndromes are recognised:

(i) Mesial Temporal Lobe Epilepsy (MTLE)

Mesial temporal epilepsy is the best known and the most frequent. Patients usually have known risk factors such as perinatal injury, central nervous system (CNS) infection, febrile seizures (FS), head trauma, and family history of epilepsy [43].

(ii) Lateral or neocortical temporal epilepsy (NTE)

NTE has a different clinical profile than mesial epilepsy. A history of FS, CNS infection, perinatal complications or head injury is less common than in patients with MTS. Seizures in patients with NTE appear five or ten years later than in MTS [43].

2.3. Magnetic Resonance Imaging (MRI)

2.3.1. Basic MRI Physics

MRI is a non-invasive method of visualising the internal structure and certain functional aspects of the body. It uses non-ionising electromagnetic radiation and utilises radio frequency (RF) radiation in the presence of carefully controlled magnetic fields to produce high-quality cross-sectional images of the body in any plane. MRI is created by placing the patient in a large magnet that induces a relatively strong external magnetic field. This causes the nuclei of many atoms in the body, including hydrogen, to align with the magnetic field.

This alignment is next perturbed by applying external RF energy at an appropriate frequency to create resonance. Spatial localisation is achieved by applying a spatially dependent magnetic field (called a gradient) while simultaneously introducing RF energy into the tissue. The gradient field selectively modulates the patient's resonant frequency in accordance with the Larmor equation.

Larmor equation is expressed as:

$\omega_0 = \gamma B_0$ Equation 2.1 Larmor equation

Where ω is the resonant frequency, γ is the gyro magnetic ratio and B is the applied filed.

Atoms with the same atomic number but different atomic weight are called isotopes, and a third property of atomic nuclei is nuclear spin. Spin is a fundamental property of nature like electric charge or mass. Single unpaired electrons, protons, and neutrons each have a spin of 1/2. When placed in a magnetic field of strength B, a particle with a net spin can absorb a photon, of frequency ν. The frequency depends on the gyromagnetic ratio, γ of the particle [44].

The nuclei return to their restive alignment through various relaxation processes, emitting RF energy proportional to the magnitude of their original alignment or magnetisation. After a reasonable time after the initial RF deposition, the emitted signals are measured.

A mathematical process called Fourier transform is used to convert the frequency formation contained in the signal from each location in the imaged plane into corresponding intensity levels, which are then displayed as grey levels in a matrix array.

The protons in the different tissues in the imaged layer align with the magnetic field at different rates, so there are differences in signal strength between the different tissues at any given time. This difference in signal strength from region to region is the basis for tissue contrast and forms the basis for interpreting the image.

2.3.2. Magnetic Resonance Contrast

The contrast of a magnetic resonance image, which determines the apparent structure we see, depends on how it is acquired, and on extrinsic and intrinsic factors. The magnetic field strength is an example of extrinsic contrast factors. Intrinsic factors include differences in signal intensity generated by particular tissues [8]. By adding radiofrequency or pulse gradients, and by careful choice of the gradient pulses within a pulse sequence, it is possible to ensure that only the coherences giving rise to the wanted signals are refocused. Normally, MRI maps the water distribution in the brain, but the useful contrast in the MRI image comes not only from the spatial variation of water density, but also from the differences between the nuclear magnetic processes known as relaxation, which are characterised for different times of relaxation. There are three relaxation times that are of primary interest in magnetic resonance imaging, T1, T2 and T2*. These describe the time constant for the return of the magnetisation to its equilibrium position, aligned along the static magnetic field of the scanner whenever disturbed (T1 relaxation), and the time constants associated with the loss of signal as soon as the magnetisation is displayed (relaxation T2 and T2*) [45].

T2*-weighted images are acquired through pulse sequences sensitive to field variations and are performed in order to take advantage of the fact that deoxygenated haemoglobin is paramagnetic, whereas oxygenated haemoglobin is not. Because deoxygenated haemoglobin causes rapid lag, T2* is longer in regions with highly oxygenated blood compared to regions with less oxygenated blood. Thus, an area with more oxygenated blood will appear more intense in the T2* weighting image when compared to an area with less oxygenated blood [46][47][48].

2.3.3. Functional Magnetic Resonance Imaging (fMRI)

Our brain is a complex network of functionally and structurally interconnected regions. Reason why MRI is often divided into structural MRI and fMRI. Here it should be said that relaxation T2* is the most relevant relaxation time to understand contrast in functional MRI images.

The structural MRI have as main goal to produce high quality images using different techniques that will emphasise certain contrast characteristics of anatomical structures and allow us to differentiate the structures. It provides information to qualitatively and quantitatively describe the shape, size, and integrity of grey and white matter structures in the brain.

The fMRI has as main goal detect, in a robust, sensitive and valid way, those parts of the brain that show an increase in intensity at the point of time at which the stimulation is applied [10].

fMRI is a fundamental non-invasive tool that helps understand brain functioning. It is based on studying the vascular response in the brain to neuronal activity and can be used to study mental activity [49]. The primary contrast mechanism exploited for fMRI is blood oxygenation level dependent (BOLD) contrast to study local changes in deoxyhaemoglobin concentration in the brain. In order to use this approach, statistical analysis of the fMRI data is critical in the production of contrast images. The activation maps are generated by calculating the t-value statistic of how different the BOLD signal is during the active condition compared to the rest condition at each voxel.

Oxygen supply in the cerebral vascular network is a complicated process involving many physiological factors associated with neuronal activities such as cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral oxygen metabolic rate (CMRO2) [48]. The mixing of these physiological adjustments in response to transient neuronal activity generates three phases of hemodynamic response. Figure 2.5 on the left indicates the state at rest, with a standard flow. Figure 2.5 on the right indicates an activated state in which there is an increase in blood flow and blood volume, resulting in an increase in blood oxygenation and a decrease in paramagnetic deoxyhaemoglobin in capillaries and venules, leading to an increase in T2* of the magnetic resonance signal.

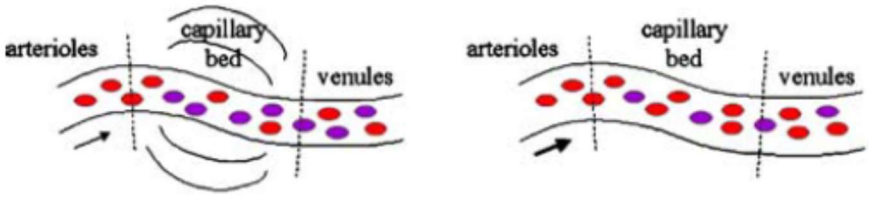

Figure 2.5: Schematic representation of contrast BOLD (in red the HbO2 and in purple the Hbr) (Retrieved from Peter Jezzard, FMRIB Centre Oxford, UK)

The magnetic resonance signal depends on the correlation between the metabolic oxygen rates (CMRO2) and CBF, which support bioelectric work in order to support neuronal excitability as well as dilation of blood vessels. The signal change relative to these physiological factors can be expressed by the following equation [50]:

$$\frac{\Delta S}{S} = M\left(\frac{\Delta CBF}{CBF} - \frac{\Delta CMRO_2}{CMRO_2}\right) - N\left(\frac{\Delta CBV}{CBV}\right)$$ Equation 2.2 Changes induced by a task

Where M and N are measurable physiological and magnetic constants and $\frac{\Delta CMRO_2}{CMRO_2}$, $\frac{\Delta CBF}{CBF}$, $\frac{\Delta CBV}{CBV}$ e $\frac{\Delta S}{S}$ are changes induced by a task.

2.3.3.1. Task-based fMRI

Task-based functional magnetic resonance imaging is a fMRI technique that can be used to detect changes in the BOLD hemodynamic response to neural activity in response to certain events [12]. BOLD fMRI is used as an indirect and non-invasive measure of brain activity while individuals perform a variety of different tasks designed to activate and identify specific functional brain regions.

There are a number of different ways that one could try to identify the different subdivisions of the human brain. One powerful approach is to examine brain regions whose activity changes when people are asked to (i) process different kinds of information (e.g., words, pictures, sounds, letters,

images); (ii) use different types of thinking skills (e.g., memory, decision-making, language generation); or (iii) respond in different ways (e.g., hand grasping, button presses) [51].

2.3.4. Hemodynamic Response Function (HRF)

The ability to accurately model the evoked hemodynamic response to a neural event plays an important role in the analysis of fMRI data. When analysing the shape of the estimated hemodynamic response function (HRF), summarising measures of psychological interest (e.g., amplitude, delay, and duration) can be extracted and used to infer information regarding the intensity, onset latency, and duration of the underlying brain metabolic activity [49].

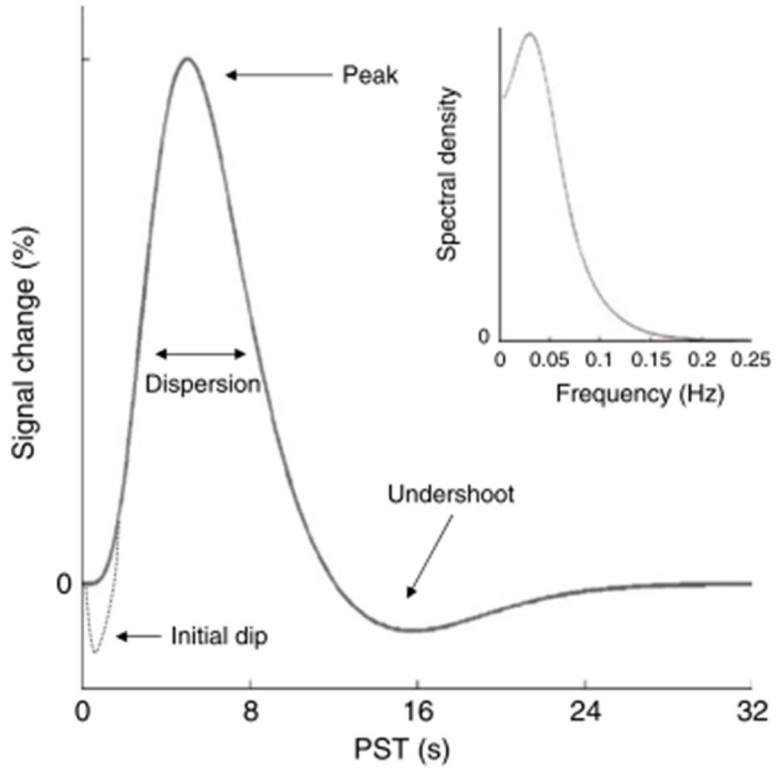

Figure 2.6: Typical (canonical) BOLD impulse response [52]

The BOLD signal is modelled by neuronal causes that are expressed via a HRF. A typical BOLD response to a single, impulsive stimulation (“event”) is shown in Figure 2.6.

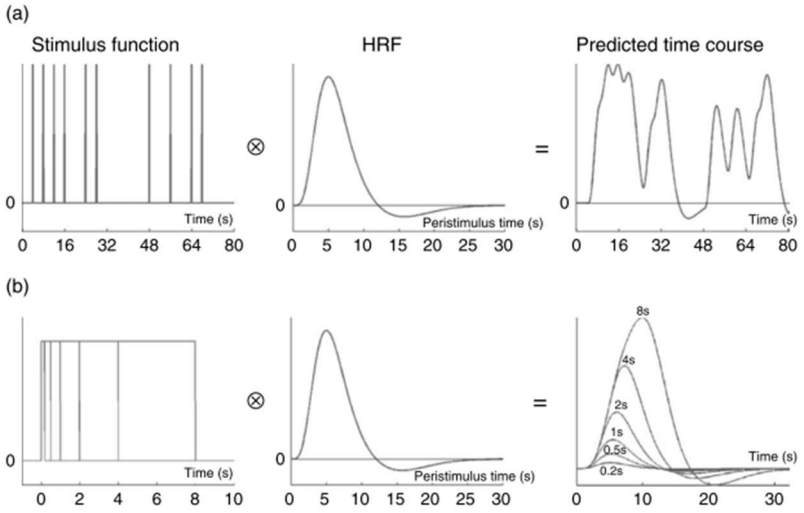

Figure 2.7: Linear convolution with a canonical HRF [52].

The result of convolving a random sequence of neuronal events with a 'canonical' HRF is shown in Figure 2.7(a) and the result of convolving a more sustained period of neuronal activity with the canonical HRF is shown in Figure 2.7(b).

2.3.5. Statistical analysis of fMRI data

2.3.5.1. General Linear Model (GLM) Analysis

Assuming a linear relationship between stimulation and BOLD response, the continuous signal produced by a specific time course of stimulation can be predicted within the GLM analysis [12].

The GLM is variously known as "analysis of covariance" or "multiple regression analysis".

$Y = X\beta + \varepsilon$ Equation 2.3 General Linear Model equation

The GLM is an equation that expresses the observed response variable in terms of a linear combination of explanatory variables X plus a well-behaved error term.

General linear modelling sets up a model and fits it to the data. If the model is derived from the timing of the stimulation that was applied to the subject in the MRI scanner, then a good fit between the model and the data means that the data were probably caused by the stimulation [10].

2.3.5.2. Independent Component Analysis (ICA)

ICA works by decomposing a two-dimensional data matrix into the time courses and associated spatial maps of the underlying "hidden" signal sources [53]. The FMRIB Software Library (FSL) used in most of the analysis here, uses 3 different types of ICA sessions in order to control some of the decomposition options. They are:

(i) Single-session ICA, which will perform standard 2D ICA on each of the input files.

(ii) Multi-session temporal concatenation, which will perform a single 2D ICA run on the concatenated data matrix (obtained by stacking all 2D data matrices of every single data set on top of each other).
(iii) Multi-session Tensor-ICA which will perform a 3D Tensor-ICA decomposition of the data.

2.3.6. fMRI experimental design

2.3.6.1. Paradigm Design in fMRI

Any fMRI clinical application involves a paradigm, a defined functional measurement, and a task that probably will activate the cortical area to be studied. Many stimulation paradigms for the activation of specific brain regions have been used for preoperative mapping. A paradigm consists typically in control and activation conditions usually triggered by an external stimulus.

Most fMRI studies involve covert verbal responses to avoid speech-related artefacts. However, overt responses can be beneficial for clinical studies, as they are useful for monitoring performance in the scanner and performing event-related analysis. The inclusion of overt responses allows for online measurement of performance, which is particularly relevant for interpreting performance and studying brain networks in people with cognitive impairment [41].

One can make a distinction between two main types of paradigms. Those which are “blocked” and those “event-related” [45], [54]. The first paradigms, “block design”, consist of a succession of blocks, each of which constitutes an activation or control condition, and typically lasts for 10 to 40 seconds [54], [55].

The “block design” is the simplest fMRI paradigm and the one more used in clinical examinations. The activation block must evoke neuronal process being investigated, whereas the control block must trigger any of the areas except the area of interest. The desired outcome is extracted by comparing the signal magnitudes of activation and control tasks [56]. This type of paradigm is statistically robust, since the signal acquired for each condition is high, and is also restrained, leaving little room for weak or unexpected stimuli.

The second, “event-related design”, arises from functional neurological studies [54]. Therefore, an “event-related design” allows for the presentation of unexpected stimuli, as well as many different conditions, making it a very flexible paradigm but less robust statistically because the signal acquired for each condition is weak [55]. It is also possible to use hybrid or mixed paradigms in order to combine parts of “blocked” and “event-related”.

2.4. State-of-the-Art

2.4.1. Temporal Lobe Epilepsy

Recent studies describing the clinical neuropsychology of TLE generally have emphasised (i) lateralisation of cognitive deficits and the material-specific model of memory and/or (ii) the relationships among pre- and post-surgery performance on standardised measures of anterograde memory, demographic and epilepsy variables and neuroimaging, neuropathology, and neurosurgery data [57].

Seizures in TLE are suggested to be multifocal, which leads to many underlying mechanisms. Some of the mechanisms that have been identified are (i) seizures due to genetic causes, (ii) seizures due to developmental disorders or malformations, and (iii) seizures that develop after a progression of changes in response to an injury [4]. Information continues to increase about the TLE and so are treatments, which include temporal lobectomy and innovative assessment techniques.

2.4.2. Memory Network in Temporal Lobe Epilepsy

Declarative memories, episodes, and facts you can consciously recall are stored and retrieved in the hippocampus but are also stored throughout the brain. Each element of a memory, the sight, sound, word, or emotion that makes it up, is encoded in the same part of the brain that originally created that fragment. Our memories are distributed throughout the brain, so even if one part of an experience is lost, many others are preserved. One advantage of such a distributed storage system is that it makes long-term memories more or less indestructible. If they were stored in a single brain region, damage to that area would completely erase the memory [26].

However, previous studies have shown that individuals with TLE have significant material-specific episodic memory impairments with greater verbal and visual memory deficits accompanying left and right TLE, respectively [8], [9]. It is more and more undisputed the appreciation of memory as a “network function”, while simultaneously it is known that mesial temporal structures have a critical role in it.

Sidhu et al. 2013 [36] found extensive bilateral extra temporal and lateral temporal reorganisation of fMRI activation during memory encoding, and also orbitofrontal cortex, anterior cingulum and insula activation, where Golby et al. 2002 [58] and Bonelli et al. 2013 [59] reinforce the importance of this medial temporal reorganisation in patients with TLE.

Based on the work done by Sidhu et al. 2013 [36] Table 2.3 is presented, indicating the regions activated during encoding and the subsequent memory effect.

Table 2.3 Activation regions during word and face encoding and subsequent memory effect

	Control subjects	***Patients with hippocampal sclerosis***
During word encoding	Prefrontal cortex, hippocampus	Temporal and extra temporal activations
Subsequent verbal memory effect	Parahippocampal gyrus, orbitofrontal cortex, fusiform gyrus	Posterior hippocampus, parahippocampal gyrus, fusiform gyrus, orbitofrontal cortex, anterior cingulate cortex
During face encoding	Prefrontal cortex and hippocampal activations	Temporal activations
Subsequent visual memory effect	Right amygdala, hippocampus, fusiform gyrus, orbitofrontal cortex	Posterior hippocampus, parahippocampal gyrus, fusiform gyrus, insula, orbitofrontal cortex, amygdala

Surgery remains an essential option for the treatment of medically intractable TLE. The main aim of epilepsy surgery is to completely resect the epileptogenic focus with little consequence on eloquent function such as vision, language, memory, sensory and motor functions [8]. However, only 66% of patients achieve postoperative seizure freedom, perhaps attributable to an incomplete understanding of brain network alterations in surgical candidates [14]. But this measure may lead to various functional deficits including an upper quadrant visual field cut, naming difficulties, and to verbal and visual memory impairment. This means that memory decline occurs after temporal lobectomy: in fact according to the literature more than 30% of patients suffers from memory decline. Bonelli et al. 2010 [60] investigated the reorganisation of memory functions in TLE in order to determine whether preoperative memory fMRI may predict memory changes following anterior temporal lobe resection with good results. From several studies it is proposed to limit the extent of hippocampal resection whenever possible.

Over the last two decades, experimental studies in memory fMRI have advanced tremendously the understating of neural correlates of the memory encoding network in healthy controls and patients [8]. Some mental illnesses may be diagnosed by brain imaging, using Computerised Tomography (CT) and MRI scans, since they are good at showing tumours and areas of damage. Functional brain imaging may be used to explore abnormal brain patterns, such as those found in epilepsy [26]. fMRI has demonstrated reorganisation of memory encoding networks within the temporal lobe in TLE [8]. Sidhu's findings suggest that memory fMRI is an evolving research method that also holds promise as a clinical tool.

2.4.3. Memory Paradigms

fMRI studies present a unique set of design parameters that need to be determined. These parameters refer to the details of the data acquisition from the scanner. The experimental design of an fMRI study is complex, as it involves important issues to psychological experiments and also issues related to data acquisition and stimuli presentation. It is important to understand that not all paradigm designs are equal and that the spacing, ordering of events, psychological nature of the task is critical for the constitution of an optimal experimental design. Furthermore, the efficiency of the subsequent statistical analysis is directly related to the experimental design, so it must be carefully considered during the design process. In general, it can be said that a good experimental design attempts to maximise the statistical efficiency and power, which are the ability to estimate the HRF and the ability to detect significant activation respectively, and psychological validity [61].

Various works done by several authors used blocked design or event-related design according to their final purpose. To the creation of the paradigm in this study, the work done by Sperling et al. 2001 [62], 2003 [63] served as inspiration to the final paradigm.

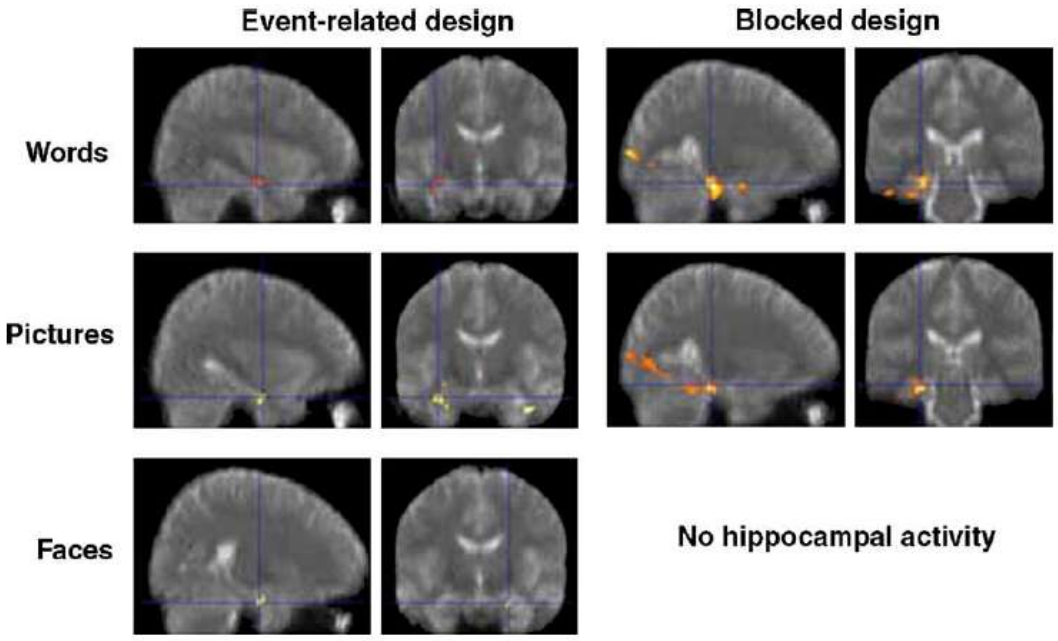

Figure 2.8: Comparison of event-related and blocked experimental design for each material type. For pictures and words, the effects of subsequent memory in the MTL, as revealed by the event-related analysis, are located more anteriorly than those revealed by the blocked analysis [64].

Powell et al. 2005 [64] used stimuli of three different material types (Pictures, Words and Faces) and showed that the difference between event-related design and blocked design is not only a matter of imaging analysis, but of cognitive model. From Figure 2.8 it is possible to identify the difference between event-related approaches, identifying encoding in anterior regions of the brain, versus blocked designs, which show apparent encoding effects in posterior regions which suggests that anterior MTL structures underlie memory encoding as judged by subsequent memory effects, and that more posterior activity detected in other fMRI studies is related to deficiencies of blocked designs in the analysis of memory encoding [64]. It is worth noting that the conclusion here by Powel et al. 2005 [64] shows clearly how important the experimental design is.

Other design experiments related to memory in TLE studies have been reported to activate regions within the MTL [60], [65], and few others have reported extra temporal subsequent memory effect activation in regions corresponding to insula, cuneus and cingulate cortex. In addition, recent studies used other paradigms like the case of the Bigras et al. 2013 [66] in which they used a design fMRI scene-encoding task, or like the case of Mechanic-Hamilton et al. 2009 [16] were they assessed memory for complex scenes using a blocked design experiment.

In another study from Zhu et al. 2021 [67] they explored quantitative measurements of the visual attention and neuroelectrophysiological relevance of memory deficits in TLE by eye tracking and EEG, concluding that eye tracking appears to be a quantitative, objective measure of memory evaluation in TLE patients. According to that study, in most circumstances, the attention module during memory tasks cannot be accurately evaluated due to lack of control for viewing behaviour assessment, but they mention Douglas et al. 2017 [68] and Wirth et al. 2017 [69] to say that eye tracking in memory paradigms were helpful in resolving this issue and separating the effect of visual attention.

The fact is that the different studies and authors have produced different experimental designs in order to optimise their statistical results, and the conclusion that can be drawn is that some intuitions and tests of design optimality can be gained from a deeper understanding of the statistical analysis of fMRI data. In fact, several methods to help researchers select the design parameters and the sequencing of events that should be used in an experiment have been presented in studies like the ones of Wagner and Nichols 2003 [70] in which they use an approach of a class of flexible search algorithms that optimise designs with respect to single or multiple measures of fitness, and Liu 2014 [71], Liu and Frank 2004 [61], in which they make models for the relation between detection power and estimation efficiency in experiments with multiple trial types.

The test-retest reliability of fMRI findings is rarely investigated, and the studies that do investigate them generally report poor reliability of brain activations. This significantly impacts the clinical utility of the paradigm. Despite advances in hardware and fMRI techniques, the sensitivity and thus reliability of fMRI in a single subject remains suboptimal [41].

In the end, the ideal memory fMRI paradigm, once designed, needs to be reproducible and validated at clinical level in which the challenge lies in the transition between “group data” and “group analysis” to clinically meaningful information at the individual patient level since there is no single “gold standard” memory fMRI protocol due to the variability in parameters to consider.

Having done the research to understand the state of the art regarding memory paradigms in TLE patients, it is clear and evident that this is a field with many studies and different approaches. But it is also clear that there is still no gold standard to follow or to perform before surgical procedures in patients with TLE so that they do not have memory deficits.

This study is relevant in the sense that it provides a new approach that shows that for there may be ways and standards that can be followed to obtain the best possible preoperative assessment.

We will demonstrate the methods used in our approach and then present the results and discussion of the study. We will then present our conclusions in terms of the paradigm-level approach that we took compared to other paradigms.

Chapter 3
Methodology

3.1. Patients

The fMRI data were collected for 12 patients who were diagnosed with TLE. Of the 12 patients, 8 (67%) were males and 4 (33%) were females. Age ranged from 25 to 62 years old. Additionally, 11 patients were Portuguese native speakers and 1 was proficient in Portuguese language. Recruitment for this study was done in the Hospital de São José, Lisbon.

3.2. Hand Grasping and Memory fMRI Paradigm Design

All patients were submitted to a hand grasping paradigm and memory paradigm. The hand grasping paradigm was presented through auditory stimuli, as we can see in Figure 3.1, while the memory paradigm was made using PsychoPy which is an open-source application that allows the presentation of stimuli and collection of data for a wide range of neuroscience, psychology, and psychophysics experiments [72].

In the hand grasping task a block design paradigm was made of 100 seconds (1 min 66 seconds) in which the patients were asked to do the task alternating the movement of the hand accordingly with given instructions, which was to alternate the movement of the hand in each 10 seconds, as shown in Figure 3.1.

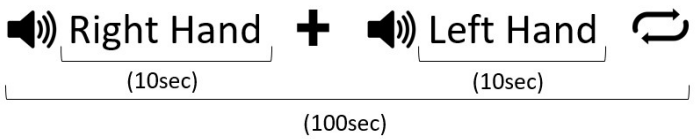

Figure 3.1 Representation of the hand grasping paradigm. The paradigm was presented through auditory stimuli.

To test patients' memory an blocked design paradigm was built using faces acquired from the Audio Visual Technologies Group (GTAV) Face Database [73] and fictional names. The task consisted of viewing faces unfamiliar to the study patients paired with fictional first names, in a modified Novel vs. Repeated design [74] as indicated in the schematic diagram of the task design shown in Figure 3.2. patients were given explicit instructions to try to remember which name was associated with which face

for later recall and to make sure they understood what the purpose of the paradigm was, a practice run was made. The total duration of the memory paradigm was 10 minutes. Each face-name pair was presented for 5 seconds, separated by a fixation cross presented in the centre of the visual field for 2.5 seconds, to focus the patients' attention on the visual domain. Patients viewed seven novel face-name pairs during each Novel block. They examined two repeated face-name pairs (one male and one female). These two repeated face-name pairs were first shown to the patient in the practice run, so they were already familiar to the patients at the beginning of the functional runs. The male and female face-name pairs alternated throughout each repeated block. A total of four runs were shown to each patient. Each run was composed by a novel block pair (≅52 seconds) followed by a fixation cross presented in the centre of the visual field (≅24 seconds) and this one was followed by repeated/same block pair (≅52 seconds).

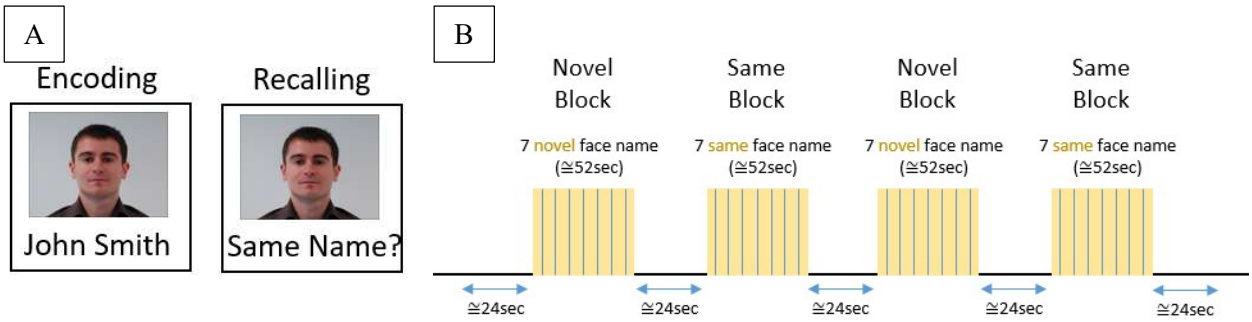

Figure 3.2 Task of viewing faces unfamiliar to the study patients paired with fictional names, in a modified Novel vs. Repeated/Same design as indicated in the schematic diagram of the task design. **A**. Face-name paired-associate paradigm. **B**. Schematic diagram of the task design for both encoding and recalling runs.

The repeated/same face-name pairs could have wrong names associated (FALSE), or correct face-names associated (TRUE), to check whether the patient remembered the correct answer or not. From an algorithm with the time series of the memory stimuli, as shown in Figure 3.5, the Figure 3.3 showing the paradigm of TRUE/RED responses and FALSE/GREEN responses was obtained.

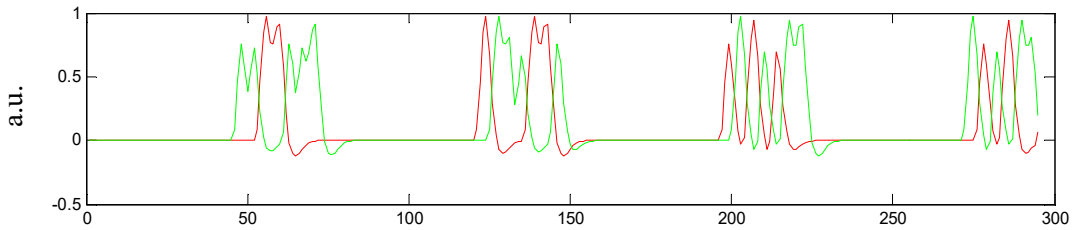

Figure 3.3 Plot with the time series of the memory stimuli. This plot shows the paradigm's TRUE /RED responses and FALSE /GREEN responses. This is indicative of the responses expected according to the paradigm.

The patients' answer was provided through hand grasping. The patient indicated whether it thought that it was the correct face-name pair through the right hand grasping and the incorrect face-name pair through the left hand grasping. This paradigm led to a blocked analysis.

The paradigms of hand grasping and memory were based on the widespread use of fMRI tasks and their ability to produce robust and reliable activation of memory-related brain regions [62][63].

3.3. Functional MRI Acquisition

Brain scans were acquired using the 1.5T *Siemens MAGNETOM Avanto* scanner with a Head Matrix Coil (12 channels) and the syngo MR B17 software housed at Hospital de São José. Head movement was minimised with the use of the cushions carefully placed between the patient's head and the head matrix coil. For each patient, an anatomical volumetric T1-weighted Magnetization Prepared RApid Gradient Echo (MPRAGE) scan was first collected. The functional acquisition was done using a T2*-weighted double-refocused spin-echo sequence with echo planar imaging readout (BOLD sequence), with the following parameters: Repetition Time (TR) = 2000 ms; Echo Time (TE) = 50 ms; Field-of-View (FOV) = 230 mm; flip angle = 90°; voxel size = 3.6×3.6×5.0 mm^3, number of interleaved slices = 21, slice thickness = 5.0 mm. This sequence was used for a 5 min Resting-State acquisition followed by the Hand Grasping Task and by the Memory Task paradigms using the same acquisition parameters.

3.4. Functional MRI Data Analysis

The data were analysed using FSL tools, MATLAB, SPM and xjView.

FSL Multivariate Exploratory Linear Optimised Decomposition into Independent Components (MELODIC) tool was used to do the probabilistic independent components analysis (ICA) for memory data and hand grasping. The FSL fMRI Expert Analysis Tool (FEAT) tool was also used for pre-processing and data analysis regarding data from hand grasping and memory. In other words, was used GLM to analyse the functional images according to the stimuli provided in the memory paradigm. More specifically the paradigm was convoluted with the HRF and used as a regressor on the FSL FEAT.

3.4.1. Denoising using ICA

Most fMRI data are likely contaminated by artefacts resulting from a number of influences, including head motion, physiological processes related to cardiac and respiratory fluctuations, and other scanner-related technical issues. Motion-correlated artefacts can bias our understanding of functional networks and their relationship with individual and group difference variables [75]. Therefore, techniques targeting the artefact removal (denoising) are addressed to data-driven approaches in order to reduce multiple noise fluctuations.

To denoise ICA components derived from memory data, the fsl_regfilt command was used [76], [77]. To do so, one had to run MELODIC tool to gain insight into unexpected artefacts or activations in the data. And then the MELODIC denoising was run using the commands "fsl_regfilt -i filtered_func_data -o denoised_data". The output file "denoised_data.nii.gz" contained the filtered and denoised data set which was then used by FEAT [78].

3.4.2. Hand Grasping ROI Analysis

The hand grasping data coming from FEAT was used to generate a binary mask with SPM ImCalc, created using the SPM tool in MATLAB environment, with a threshold of 4 to be applied in the memory data after proceeding to a conversion of 4D memory images into series of 3D memory images using the fslsplit utility. The hand grasping mask and the 3D memory images were subjected to an algorithm in order to perform a Mask Region-of-Interest (ROI) calculation, which aimed to perform a temporal clustering analysis (TCA) to derive the time series means associated to each mask's voxels. An example of the referred algorithm is showed in Figure 3.4.

```
masklist ={'left.nii','right.nii'};

% File with the subject data
files = dir('zfilt*.nii');

for i=1:length(files)

% Prepare the subject's data to be analysed
filelist = files(i).name;
cell_file = {filelist};
subject = filelist(1:(length(filelist)-4));


%   Creates tables of values such as mean or standard deviation for
%   regions of interest (ROIs) or counts voxels within a given range.
%   A set of p ROIs is applied to a set of q image files in order to
%   calculate r values of interest, resulting in p*q*r values to be
%   logged. Voxel exclusion criteria can be specified, which can also
%   be used to count the number of included or excluded voxels within
%   a given value range.
%   All images and ROIs must be of the same dimensions, voxel size,
%   and orientation. If need be, reslice your images before running
%   this script using e.g. SPM's realign->reslice (images 2..n).
log_roi_batch(cell_file,masklist,'zthres16_timeseries.txt', 'subject', subject,
'ignore',0, 'low_cutoff', 0,'high_cutoff',4096,'log', {'mean', 'std','included'});

end
```

Figure 3.4 MATLAB code to perform a Mask ROI Calculation.

The TCA algorithm was then used, as can be seen in Figure 3.5, Figure 3.6 and Figure 3.7, in order to obtain plots containing the time series of the memory stimuli. That is, this algorithm built the memory time series associated with each hand from the averages obtained from the Mask ROI Calculation.

```
% clear all; close all; clc;

RT=2.0;
hrf=spm_hrf(RT);

%%%% Memory paradigm (correct/incorrect <=> right/left hand) dependent on the subject
% be aware that the stimulus presentation time may not match the
% signal sampling rate (TR=2s). need to correct number of initial zeros
% (corresponds to the cross of the stimulus in the paradigm)

paradigm_true=[zeros(867,1);zeros(50,1);zeros(25,1);zeros(50,1);zeros(25,1);ones(50,1);...
    zeros(25,1);ones(50,1);zeros(25,1);zeros(50,1);zeros(25,1);zeros(50,1);zeros(25,1);...
    zeros(50,1); zeros(1009,1);ones(50,1);zeros(25,1);zeros(50,1);zeros(25,1);zeros(50,1);...
    zeros(25,1);zeros(50,1);zeros(25,1);ones(50,1);zeros(25,1);ones(50,1);zeros(25,1);...
    zeros(50,1);zeros(1009,1);ones(50,1);zeros(25,1);zeros(50,1);zeros(25,1);ones(50,1);...
    zeros(25,1);zeros(50,1);zeros(25,1);ones(50,1);zeros(25,1);zeros(50,1);zeros(25,1);...
    zeros(50,1);zeros(1009,1);zeros(50,1);zeros(25,1);ones(50,1);zeros(25,1);zeros(50,1);...
    zeros(25,1);ones(50,1);zeros(25,1);zeros(50,1);zeros(25,1);zeros(50,1);zeros(25,1);...
    ones(50,1);];
memoria_true = downsample(paradigm_true,20); % for the 300s to put 20 / for the 600s to put 10

%%%% Convolution of the time series stimulus vector with the HRF vector
convol_memoria_true=conv(memoria_true,hrf,'full');

% Choice of TR, hrf and convolution calculation with spm_Volterra (preferred)
% these are necessary definitions for the spm_Volterra-function
U.u=memoria_true;
U.name={'reg'};
bf=spm_get_bf;  % create a basis function, in this case the hrf
convreg_true=spm_Volterra(U,bf.bf);


paradigm_false=[zeros(867,1);ones(50,1);zeros(25,1);ones(50,1);zeros(25,1);zeros(50,1);...
    zeros(25,1);zeros(50,1);zeros(25,1);ones(50,1);zeros(25,1);ones(50,1);zeros(25,1);...
    ones(50,1); zeros(1009,1);zeros(50,1);zeros(25,1);ones(50,1);zeros(25,1);ones(50,1);...
    zeros(25,1);ones(50,1);zeros(25,1);zeros(50,1);zeros(25,1);zeros(50,1);zeros(25,1);...
    ones(50,1);zeros(1009,1);zeros(50,1);zeros(25,1);ones(50,1);zeros(25,1);zeros(50,1);...
    zeros(25,1);ones(50,1);zeros(25,1);zeros(50,1);zeros(25,1);ones(50,1);zeros(25,1);...
    ones(50,1);zeros(1009,1);ones(50,1);zeros(25,1);zeros(50,1);zeros(25,1);ones(50,1);...
    zeros(25,1);zeros(50,1);zeros(25,1);ones(50,1);zeros(25,1);ones(50,1);zeros(25,1);...
    zeros(50,1);];
memoria_false = downsample(paradigm_false,20); % for the 300s to put 20 / for the 600s to put 10
convol_memoria_false=conv(memoria_false,hrf,'full');
U.u=memoria_false;
U.name={'reg'};
bf=spm_get_bf;  % create a basis function, in this case the hrf
convreg_false=spm_Volterra(U,bf.bf);
```

Figure 3.5 Temporal Clustering Analysis algorithm with the time series associated to the memory stimuli.

As shown in Figure 2.7, the result of convolving a sequence of neuronal events with a canonical HRF, results in a predicted time course, as shown in the top plot of Figure 3.7.

```
%%% Set up plots
figure(99);
clf;
subplot(4,2,1);
plot(convreg_true);% convolve memorie with the hrf
grid on;
legend('Serie temporal do estimulo da memoria true');
axis([0 300 -0.2 1.2]);
xlabel('Time (seconds)');
ylabel('Stimulus');

subplot(4,2,2);
plot(convreg_false);  % convolve memorie with the hrf
grid on;
legend('Serie temporal do estimulo da memoria false');
axis([0 300 -0.2 1.2]);
xlabel('Time (seconds)');
ylabel('Stimulus');

subplot(4,2,3);
% Here it is necessary to import the time series data obtained
% after performing the average in Mask_ROI_Calculation
plot(memoria_ts_l);
grid on;
legend('Serie temporal dos dados do paciente R');
%axis([0 50 -0.2 1.2]);
xlabel('Time (seconds)');
ylabel('fMRI signal');

subplot(4,2,4);
plot(memoria_ts_r);
grid on;
legend('Serie temporal dos dados do paciente L');
%axis([0 50 -0.2 1.2]);
xlabel('Time (seconds)');
ylabel('fMRI signal');
```

Figure 3.6 Code regarding the algorithm for deriving the time series associated to the memory stimuli.

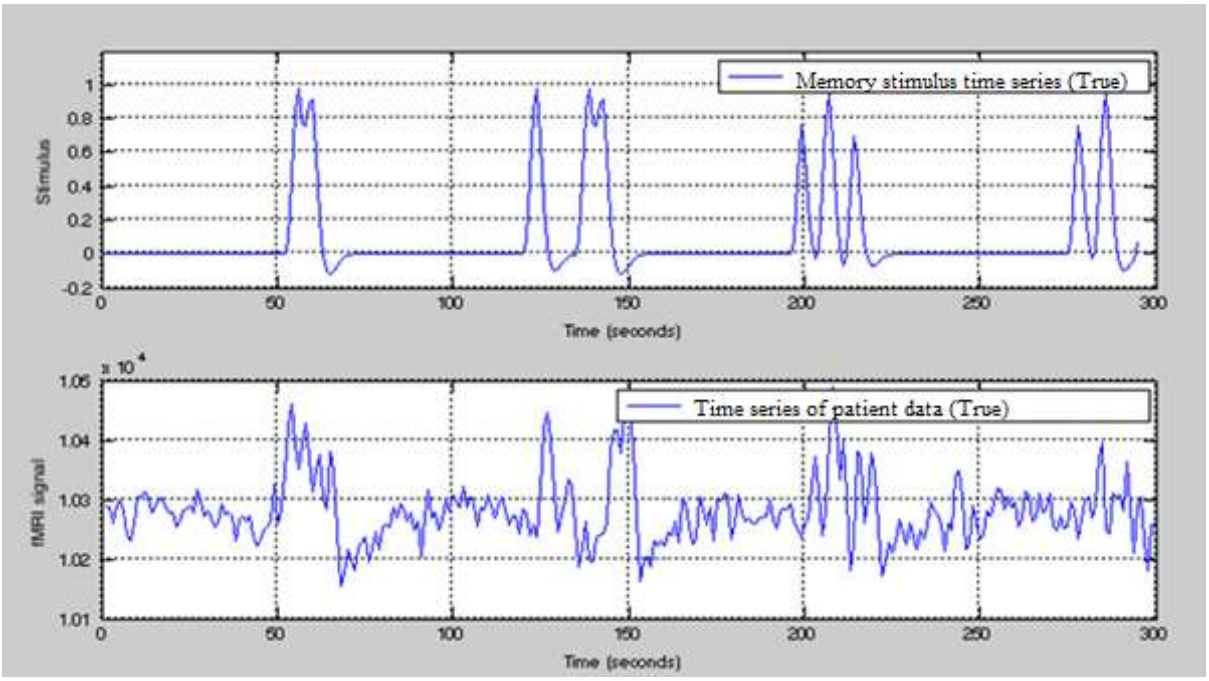

Figure 3.7 Plots resulting from algorithm with the time series associated with the memory stimuli. Paradigm's memory stimuli time series (top). Patient's time series data (bottom).

3.4.3. Reference Time Courses (RTCs)

To understand whether the responses provided by the patients were correct or incorrect, data referring to the paradigm's memory stimuli time series were first used. These data were obtained through the TCA algorithm shown in Figure 3.5.

Then, the algorithm presented in Figure 3.6 was used with the patient's time series data and the paradigm's memory stimuli time series, to generate two plots, as shown in Figure 3.7, to serve as a comparison between these two time series.

With the patient's time series data, a map was defined. Here, through the patient's time series data, the threshold from which an fMRI signal would be accepted as part of the response was empirically defined, considering the patient time series means and standard deviations. The threshold corresponds to the limit at which an event is considered to occur. The defined map was named reference time courses (RTCs) which are columns/histogram that represent individual histograms of significant activity increases for the voxels whose maximum signal increase occurred at an exact time point. RTCs x-axis represent the time points, with the columns/histogram in which the maximum signal increase occurred in red.

The evaluation of the RTCs histogram was accomplished by running the "hrf_threshold.m" algorithm for each patient, as shown in Figure 3.8. That was necessary to obtain the two-dimensional map (hist2d), through the Equation 3.1. Where the *threshold* corresponds to the limit at which an event is considered to occur in the *M* time course and is equal to 2 standard deviations above the baseline of that voxel. From there, Figure 3.9 was obtained, which presents the paradigm's memory stimuli time series plot on top, the patient's time series data plot at the middle and the RTCs evaluation plot at the bottom.

To obtain this two-dimensional map, RTC histogram, the following equation was used:

$$RTC\ histogram = \begin{cases} hist2d + 1, if\ M_i \geq threshold \\ hist2d + 0, if\ M_i < threshold \end{cases}$$

Equation 3.1 reference time courses (RTCs) histogram

The RTCs should indicate whether the answers provided by the patients were correct or not. The columns/histogram in which an event was considered to have occurred (Figure 3.9 bottom) were compared with the paradigm's memory stimuli time series (Figure 3.9 middle), so that the correct responses could be marked in green and the incorrect responses given by the patient in orange.

```
data = memoria_ts_r;

% -With 2 clusters
idx = kmeans(data,2,'EmptyAction','singleton');

mean1 = mean(data(idx==1));

mean2 = mean(data(idx==2));

means = [mean1 mean2];

mean_data = min(means);

% -activation select
% X - Can be 1; 1.5 ; 2?
X = 2 ;
threshold = mean_data + X*std(data);
Nt=300;
figure, plot(1:Nt,data),hold on,line([1 Nt],[threshold threshold]),
line([1 Nt],[mean_data mean_data])
array_de_activacao=zeros(1,Nt);
for i=1:Nt
%Conditions' verification:
if data(i) > threshold
     array_de_activacao(i) = 1;
else
     array_de_activacao(i) =0;
end

end

figure(109),imagesc(array_de_activacao)
```

Figure 3.8 Algorithm that makes the Reference Time Courses (RTCs) evaluation.

And with the plots of this algorithm was possible to do the comparison between patient responses and the correct answers. An example of the comparison is presented in Figure 3.9.

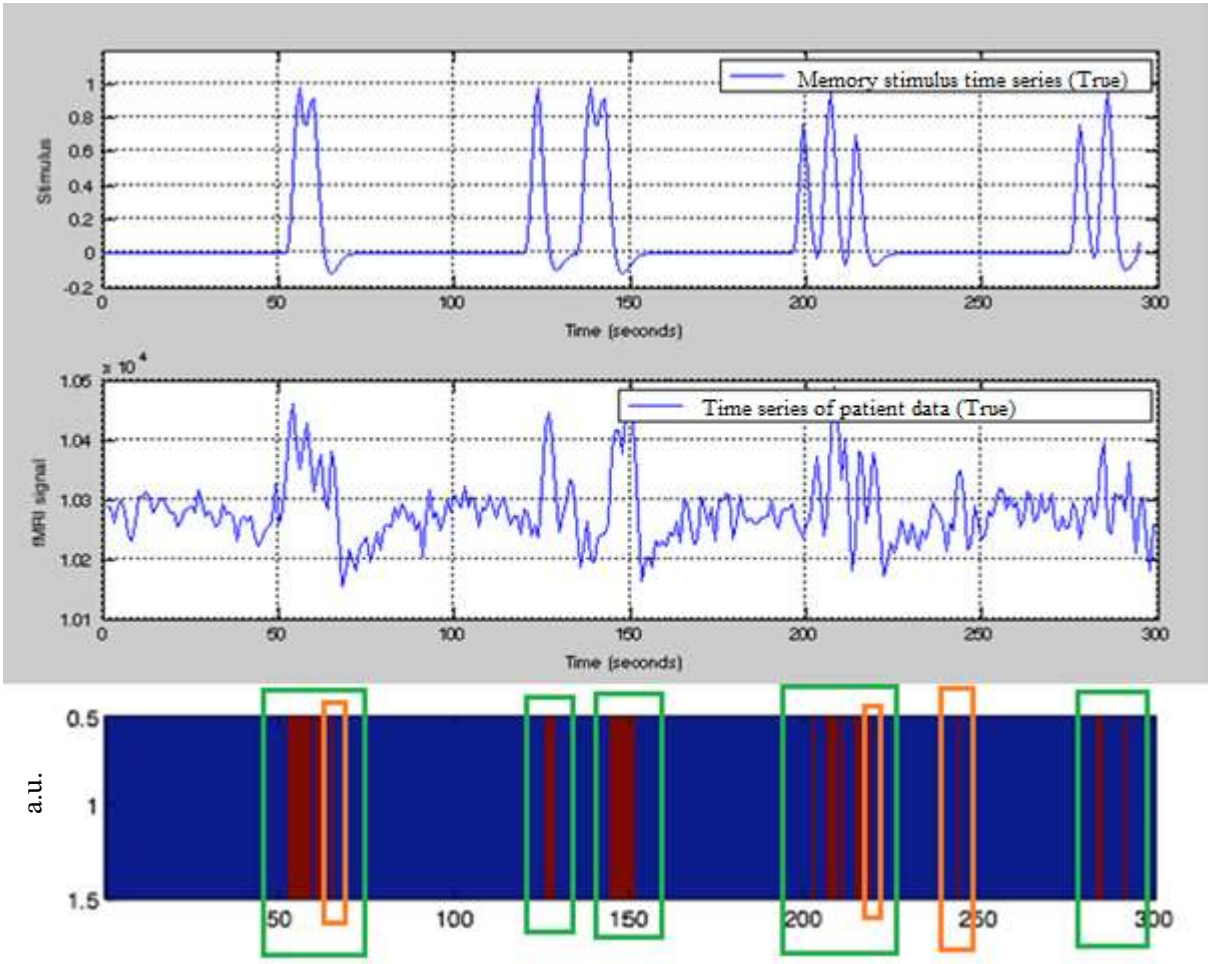

Figure 3.9 Paradigm's memory stimuli time series (top). Patient's time series data (middle). Reference Time Courses (RTCs) evaluation plot (bottom). Green colour shows correct answers and orange colour shows incorrect answers.

Subsequently the patients time series means were used as a regressor in a FSL FEAT procedure to understand which other regions may be associated to memory, as can be seen in Figure 3.10. FEAT which is a software tool for high quality model-based fMRI data analysis, with an easy-to-use graphical user interface (GUI). The data modelling which FEAT uses is based on GLM, otherwise known as multiple regression [79].

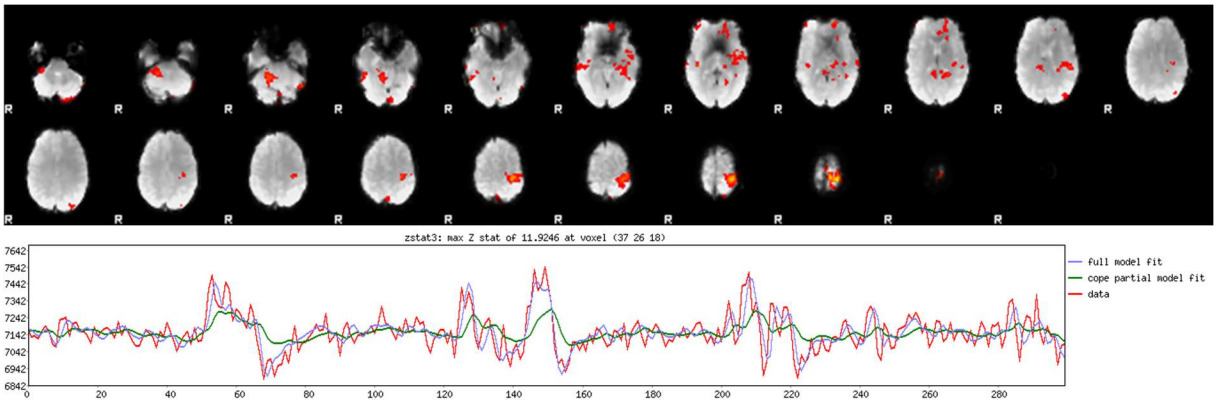

Figure 3.10 FEAT thresholded activation images. Axial slices with a quick overview of where the significant clusters are located (top). FEAT output. Time series plots (bottom).

3.4.4. Quantitative Data Analysis

A quantitative analysis was carried out, to help understand what the results meant. This was accomplished through the RTCs correct and incorrect answers provided by the patients.

Then, the necessary quantitative analysis was performed to better understand the answers given by the patients. For each of the patients, the analysis was performed to see which were the correct and incorrect answers they had given.

From these results, the percentage of correct answers (%RC) was calculated for TRUE and then for FALSE. Where PCA is the number of patient's correct answers.

$$\%RC = \frac{PCA}{Total\ number\ of\ face\ name\ pair}$$ Equation 3.2 Percentage of correct answers

Then the total percentage of correct answers (%TRC) was calculated. Where PIC is the number of patient's incorrect answers for each condition TRUE or FALSE as per the Equation 3.3.

$$\%TRC = \frac{PCA\ (TRUE) + PCA\ (FALSE)}{PCA\ (TRUE) + PCA\ (FALSE) + PIC\ (TRUE) + PIC\ (FALSE)}$$ Equation 3.3 Total percentage of correct answers

In this group analysis, patients with TRC below 40% of correct answers were classified as being in the Low Global Score (LGS). Patients with TRC values between 40% and 70% were classified as Medium Global Score (MGS). And patients with a TRC of 70% to 100% were classified as patients with High Global Score (HGS).

Afterward, there was a comparison with the results found in the literature for a better perception of the accuracy level.

Then, another quantitative analysis was performed, this time considering the anatomical regions that denoted greater activation. For this, xjView, which is an SPM add on, was used to get a better sense of the structural anatomy of a cluster of voxels and of multiple clusters and subsequently the summary of all activation regions and their names [80]. To do so, the patient data was inserted in xjView. Then the display intensity "Only+" option was chosen. After selecting the images, the significance was set to "appropriate values", meaning that they only had the necessary voxels and minimum noise. Afterwards the "slice view" was selected such that the different views (cross/coronal/sagittal) could be observed. Then the report with all the anatomical parts was obtained via one of xjView's reporting features. Having information on the anatomical regions, the data were compared between patients in order to understand what the patterns between those who had better performance and those who had worse performance were.

After designing the fMRI paradigm for hand grasping and memory, we proceeded to data collection and performed several analyses with the obtained data to best assess the robustness of our paradigm. Now that we had all the necessary elements, we were able to review and further discuss the results, as can be seen in the following chapter.

Chapter 4
Results and Discussion

The goal of this study was to assess the functional network associated to memory in patients with TLE.

The hypothesis to be tested is whether it is possible to achieve the same level of accuracy using the hand grasping and memory paradigm carried out in this study as it is when using other paradigms, such as those using buttons to respond to stimuli. And from the results of this study, we can see if we can conclude that the paradigm used is valid compared to what is in the literature. If it is valid, it can be an asset for preoperative assessment in hospitals where there are no other means to do this assessment.

In this study, fMRI was used to study the memory encoding and retrieval in patients with TLE. The hand grasping paradigm used in this study was a robust behavioural paradigm that we have encountered and previously used to examine other brain functions, namely motor regions for presurgical planning. For the memory paradigm, stimuli such as words and faces were used in an block design paradigm. The patients with TLE encoded these stimuli, viewing unfamiliar faces pared with fictional names.

The functional images from the patients in this study were used to perform a GLM analysis, which was used to configure a model that would allow describing the stimulation and linear combination of the modelled response. More specifically, the paradigm was convoluted with the HRF and used as regressor on the FSL FEAT.

4.1. Reference Time Courses (RTCs) evaluation

From the hand grasping activation maps, a mask was defined to be used in the memory images in order to obtain the HRF from the answers of the patients corresponding to the correct and incorrect answers.

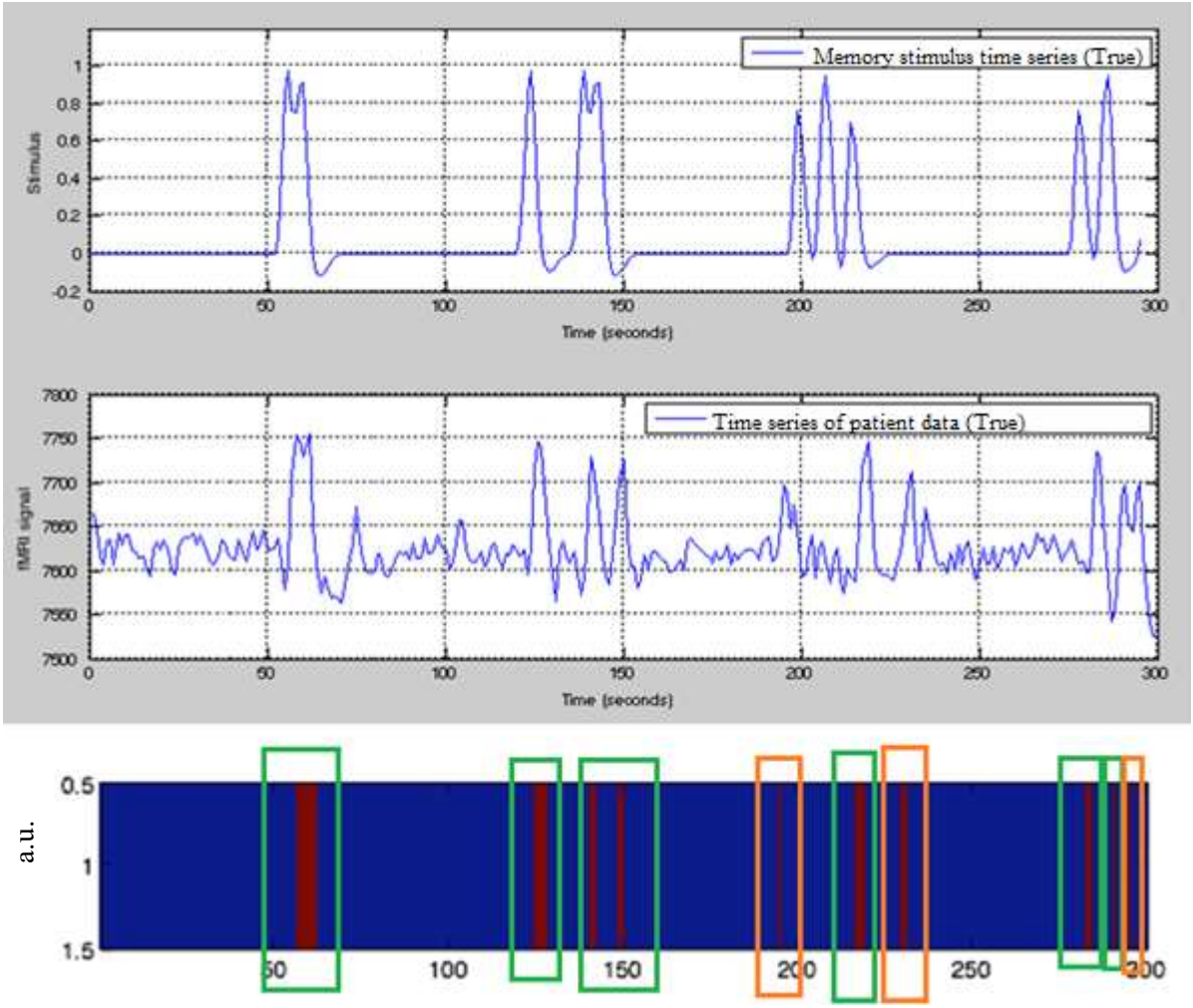

Figure 4.1 Paradigm's memory stimuli time series (top). Patient's time series data (bottom). Reference Time Courses (RTCs) evaluation plot (bottom). Green colour shows correct answers and orange colour shows incorrect answers.

We can see in the top plot of Figure 4.1 the representation of the time series of the memory stimuli for the TRUE answers. In the middle plot of Figure 4.1 we can observe the time series of the patient's data corresponding to the TRUE answers. In the bottom plot of Figure 4.1, it is possible through RTCs to analyse which were the correct responses of the patient compared to the expected.

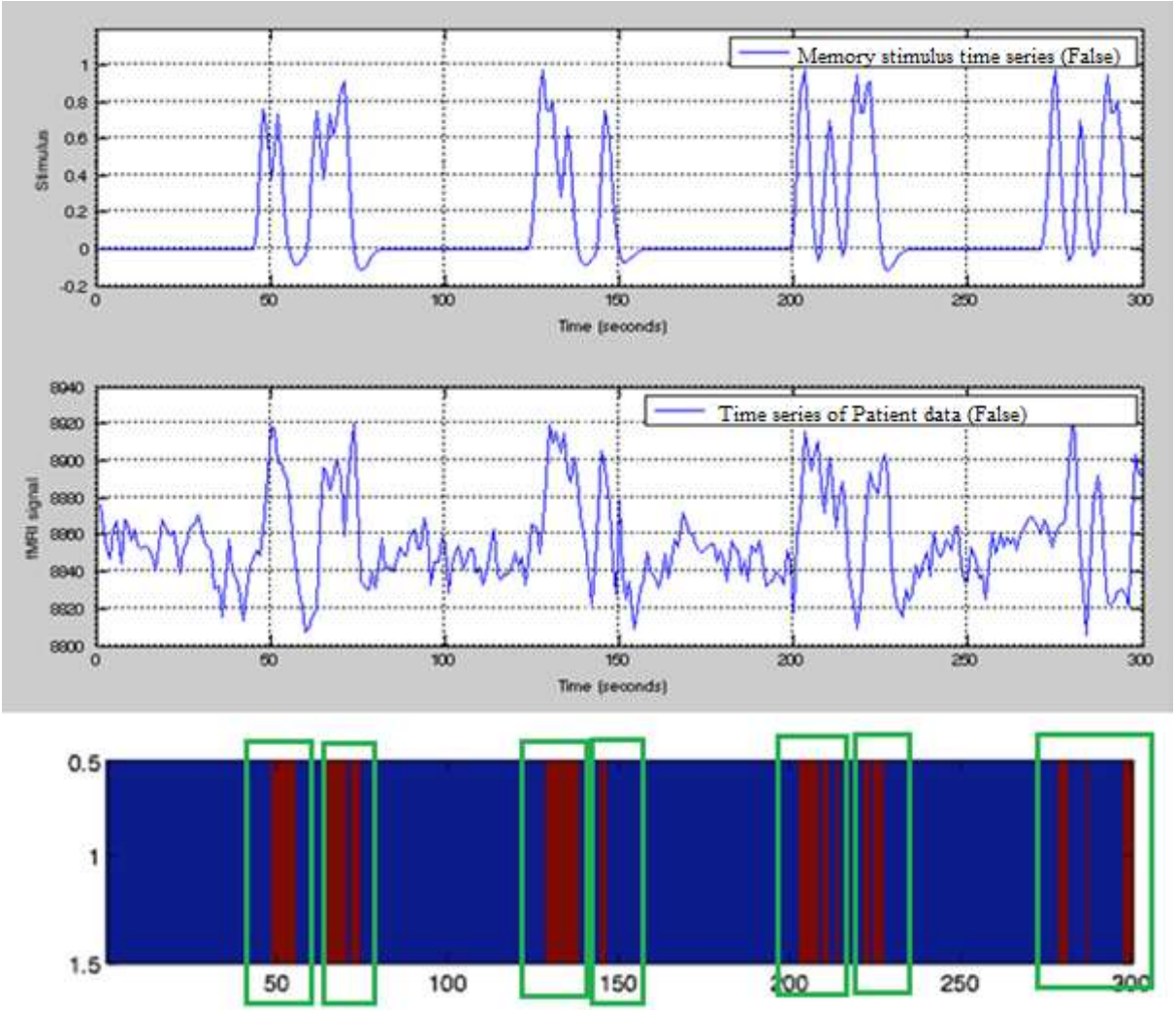

Figure 4.2 RTCs plot with answers that were FALSE for the stimuli (top) and patient response (middle). Green and orange boxes are shown for correct and incorrect answers, respectively (bottom).

We can see in the top plot of Figure 4.2 the representation of the time series of the memory stimuli for the FALSE answers expected. In the middle plot of Figure 4.2 we can observe the time series of the patient's data corresponding to the FALSE answers. In the bottom plot of Figure 4.1, it is possible through RTCs to analyse which were the correct responses of the patient compared to the expected.

For this patient, it is possible to see that he understood what was requested by the study and it seems that he does not have a memory deficit, considering only the number of correct vs incorrect answers. At the level of responses to TRUE, it starts with correct responses, but throughout the paradigm the number of correct responses seems to decrease as shown in the bottom of Figure 4.1. In terms of responses to FALSE, it seems to have a better performance, correctly answering more questions as shown in the bottom of Figure 4.2.

By finding the RTCs of each one of the patients followed by the attempt to understand where they have the same columns that represent individual histograms of significant increases for the voxels whose maximum signal increase occurred at an exact time point, and by the use of the algorithm shown in Figure 3.8, it was possible to reach the result seen in the bottom plots of Figure 4.1 and Figure 4.2. This is what we expect to be the representation of the correct answers done by the patients.

By using the FSL FEAT procedure, it was possible to understand which regions can be associated with memory. The top of Figure 4.3. shows the activated regions associated with TRUE. Although we have the information given in the top of Figure 4.3. and Figure 4.4, we have left the deeper analysis of the images and the associated regions to subsection 4.3 Anatomical Regions. At this point it is interesting to pay more attention to the bottom of Figure 4.3, which shows that for TRUE responses patients were able to give answers through hand grasping (red data) that were very close to the full model fit of the memory paradigm. This was a good way to validate whether the responses obtained were expected or not. Because FEAT automates as many analysis decisions as possible and allows easy analysis of simple experiments, while providing enough flexibility to allow sophisticated analysis of the most complex experiments, the results obtained can be relied upon to be robust, efficient and valid as mentioned in the FSL FEAT guide [79].

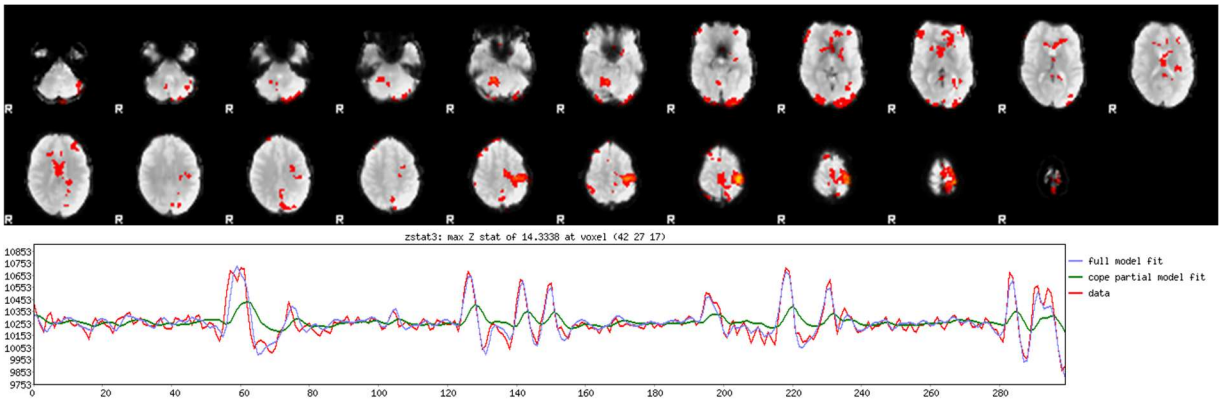

Figure 4.3 First-level FEAT analysis thresholded activation images for TRUE responses. Axial slices displaying where significant clusters are located (top). First-level FEAT analysis output for TRUE responses. Time series plot (bottom)

The bottom of Figure 4.4 shows that in the responses to FALSE, the patients were also able to give responses through hand grasping (red data) that were very close to the full model fit of the memory paradigm.

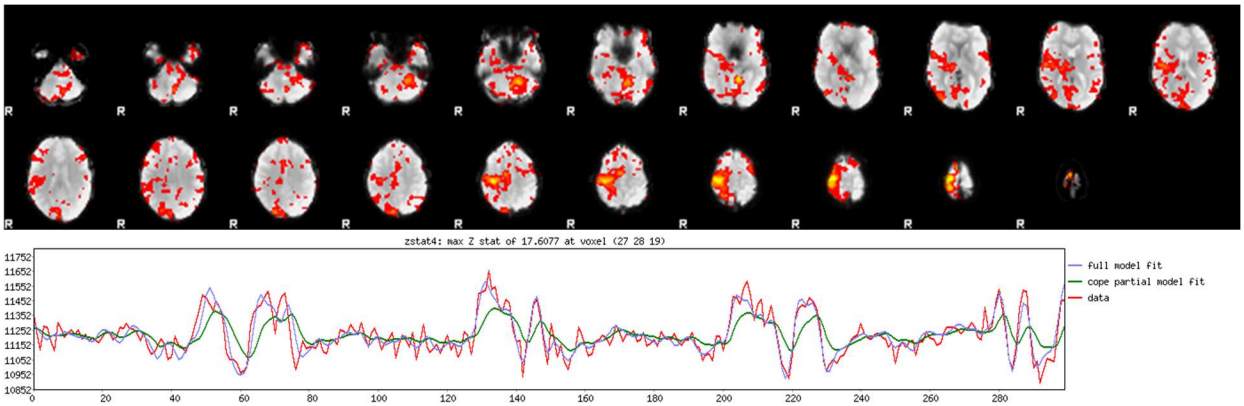

Figure 4.4 First-level FEAT analysis thresholded activation images for FALSE responses. Axial slices with a quick overview of where the significant clusters are located (top). First-level FEAT analysis output for FALSE responses. Time series plot (bottom).

From these results obtained through the FSL FEAT and looking at all patients, those who answered more questions correctly, i.e., those who performed better when examined in the RTCs, both for TRUE and FALSE presented a time series plot for TRUE and FALSE, which already gave an

indication of the patient's success or failure in terms of the answers given. This is due to the similarity or dissimilarity of the data obtained compared to the full model fit. But to confirm that what was observed in the time series plot and in the RTCs was transversal for the patients, we did a quantitative data analysis, as can be seen in the following subsection.

4.2. Quantitative Data Analysis

Through a quantitative analysis, considering all the patients of the study, it was possible to reach some results. As mentioned in the Hand Grasping and Memory fMRI Paradigm Design, the repeated face-name pairs could have wrong names associated (FALSE), or correct face-name associated (TRUE). To check whether the patient remembered the correct answer or not, the patient would have to indicate which matched the TRUE condition and which matched the FALSE condition. It should be noted that the same patients who responded to the TRUE conditions responded to the FALSE conditions. For the results to be accepted as correct answers, the RTC evaluation indicated in subchapter 4.1 was carried out. The thresholds for the cases in which we present the results as being satisfactory were defined in this dissertation, not having, in this case, any other study as a reference

Observing only the correct answers, related to the TRUE condition, without considering the incorrect answers, we could observe that 16.7% (2 patients) of the patients got all the questions right. 25% (3 patients) correct answers in a range of 75% to 99%, as well as 25% (3 patients) of correct answers in a range of 50% to 74% of the answers. A third of the patients, that is, 33.3% (4 patients) of the patients, had the level of correct answers in the range between 25% and 49%. None of the patients responded below 25%, as shown in Figure 4.5.

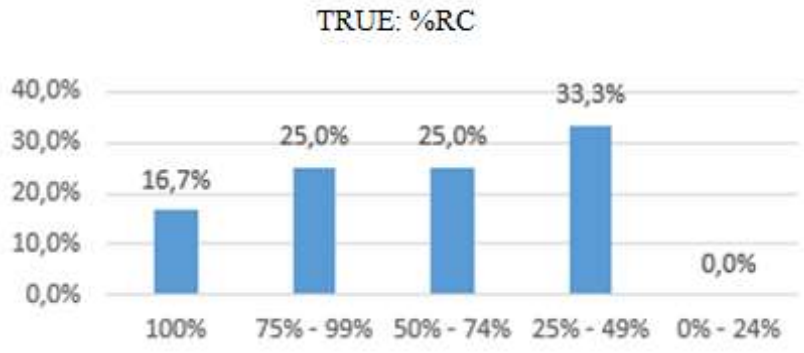

Figure 4.5 Percentage of patients who correctly responded to the TRUE part of the paradigm (Names and faces that were correct and the patient said they were correct). %RC - the percentage of correct answers to TRUE.

Now moving on to the observation of the responses in relation to FALSE, what we can denote from Figure 4.6 that two-thirds of the patients managed to respond correctly. 25% (3 patients) answered correctly to everything, 25% (3 patients) answered correctly between 75% and 99% and 16.7% (2 patients) answered correctly between 50% and 74%. Therefore, a third of the patients (4 patients) responded unsatisfactorily, i.e., below 50%.

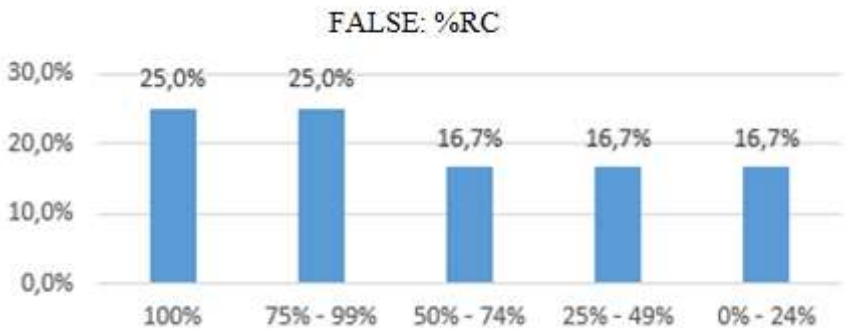

Figure 4.6 Percentage of patients who correctly responded to the FALSE part of the paradigm (Names and faces that were not a match/incorrect and the patient said they were incorrect). %RC - the percentage of correct answers to FALSE.

However, as can be seen in Figure 4.7, from the perspective of the Global Average of TRC (total percentage of correct answers, counting both correct and incorrect answers) we can see that none of the patients were able to answer all the questions. Half had a rate of 75% to 99% of answers correct, none had 50% to 74% of all answers correctly.

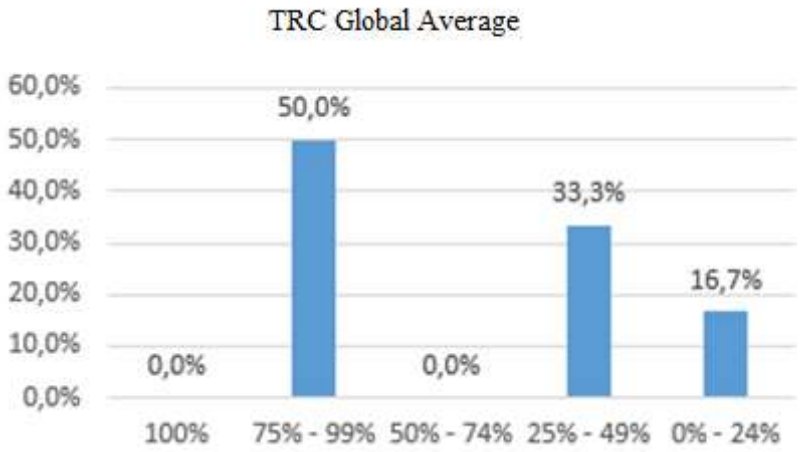

Figure 4.7 TRC Global Average - total percentage of correct answers, counting both correct and incorrect answers.

Making a comparative study with the literature at the level of accuracy, we were able to find the following.

For the study by Paul F. Hill et al. 2020 [81], it is noted that for the group with TLE, the “Hit Rate” (equated to the TRUE condition in this dissertation) has an average of 78%, while for the “False Alarm Rate” (equated to the FALSE condition in this dissertation) it has a percentage of 41%, that is, patients with TLE had a higher level of correct answers than incorrect answers.

The same can be seen in this dissertation, where patients with TLE had a higher level of correct answers than incorrect answers. In this case, there were 57% (7 patients) with correct answers and 43% (5 patients) with incorrect answers.

When compared with the study by Sidhu et al. 2013 [36], we can consider the results of both the control group and the patients with hippocampal sclerosis. The control group performed significantly better than patients with hippocampal sclerosis.

Note here that in the results of this Dissertation a paradigm was made with Face & Name (word) together, but in the study by Sidhu et al. 2013 [36] they studied face recognition and word recognition separately. It's observed a greater word recognition than face recognition. For faces, patients had an average of (49% for left hippocampal sclerosis and 59% for right hippocampal sclerosis) 54% accuracy and for faces only (15% for left hippocampal sclerosis and 14% for right hippocampal sclerosis) 14.5%. In the performance in word recognition, patients showed to hit more correct answers than wrong, in the face recognition task it was the opposite.

Some studies [82], [83], state that given the role of the hippocampus in TLE, a paired-associate memory paradigm, such us face-name association, may be most appropriate for the investigation of hippocampal-dependent memory. So, by joining the Face to a name (word) the accuracy level has the potential to increase, reaching the same levels seen here in our study.

4.3. Anatomical Regions

4.3.1. Hand Grasping

As mentioned in the methodologies in Chapter 3.2, all patients were submitted to a hand grasping paradigm. The hand grasping paradigm was presented through auditory stimuli, as shown in Figure 3.1.

From the hand grasping paradigm, it was observed that the right hand (which was used in the memory paradigm to indicate that it was the correct face-name pair) and the left hand (which was used in the memory paradigm to indicate which was the incorrect face-name pair) there was significant clusters of activity in motor area. There was also significant activity in auditory areas, namely the temporal lobe.

As shown in Figure 4.8, during the hand grasping of the right hand, the left cerebrum was active, more specifically in motor regions such as brodmann area 3 (primary somatosensory cortex (postcentral gyrus)), brodmann area 4 (primary motor cortex (precentral gyrus)) and brodmann area 6 (premotor and supplementary motor cortex). Also, the Supp_Motor_Area_L (aal) and Precentral_L (aal) were activated, being responsible for executing voluntary movements, but also in the auditory cortex, namely the temporal lobe, which processes auditory information. There is also activation of the frontal lobe, which is important for voluntary movement [84]. A cluster of activity was also observed in the midbrain, which serves important functions in motor movements and in auditory processing [85].

Additionally, it can be seen in Figure 4.8 that when hand grasping the left hand, there is activity in the Right Cerebrum, more specifically in the frontal lobe. But in this case, there was also some activity in Left Cerebrum. Meaning that the involved network is not entirely right-lateralized, as in the previous case for the right hand, with left lateralization. This may be due to the fact that for this patient the left hand is not the dominant hand [86]. There was also activation of the motor and auditory regions such as right hemisphere in the Brodmann area 6 (Premotor and supplementary motor cortex), Supp_Motor_Area_R (aal), Precentral_R (aal) and Midbrain. Hippocampus_L activation was observed as well. The hippocampal interactions with the motor system are often assumed to reflect the role of

memory in motor learning. The hippocampus shows motor activity, especially during motor sequence learning [87].

Figure 4.8 on the bottom shows the paradigm full model plot fit in blue and the patient's response in red. Here, it is important to point out that the data show that all patients were able to correctly execute the hand grasping paradigm.

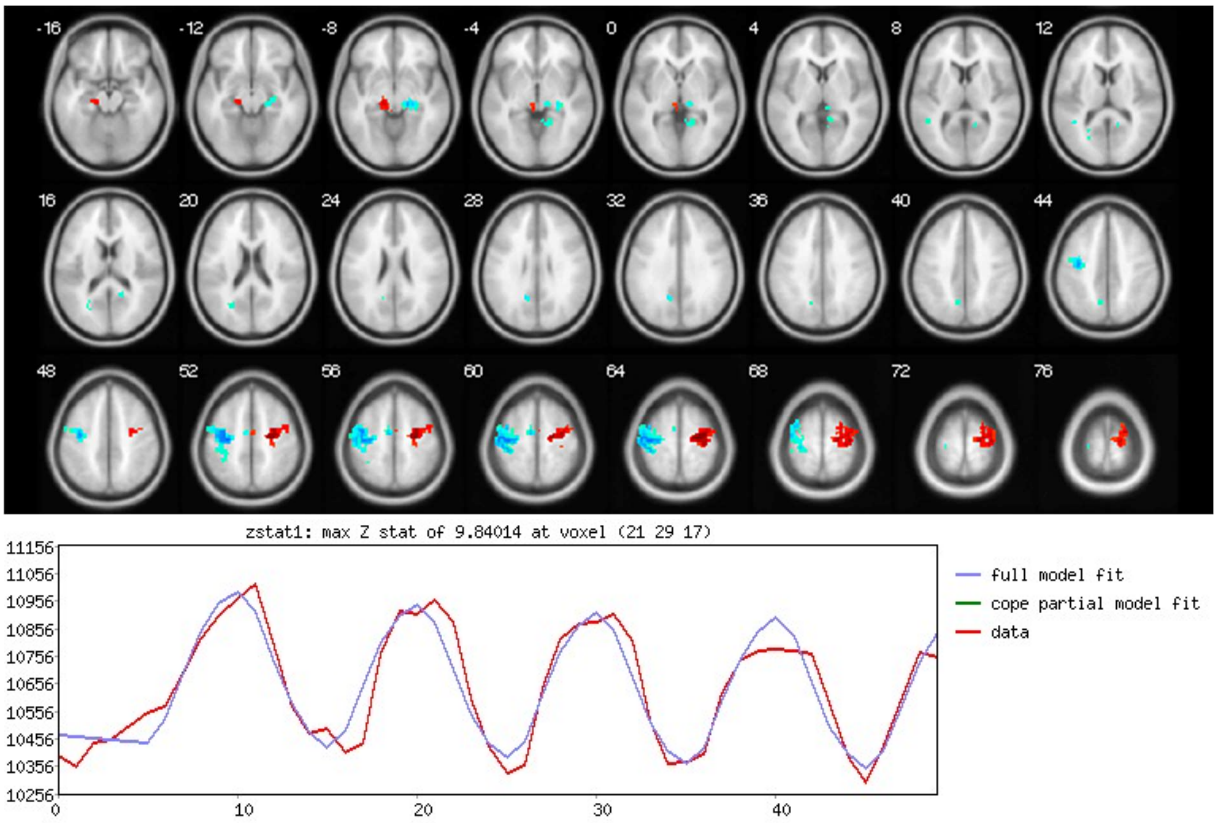

Figure 4.8 Single patient cluster of activity related to the hand grasping paradigm, performed before the memory paradigm. At the top is a patient's transverse plane image with blue activation of the left cerebrum and red activation of the right cerebrum due to hand grasping of the right and left hands respectively. On the bottom, the paradigm full model plot fit can be seen in blue and the patient's response in red.

4.3.2. Memory

Through the analysis of the anatomical regions, we tried to understand which anatomical regions are similar among the patients that have activation. We analysed the patterns between those who had the best and worst performances. We did a comparative study with what exists in the literature.

In Figure 4.9 it is possible to observe the activation of the Left Temporal Lobe during the response to one of the activities of the paradigm, more specifically during the answers that were TRUE.

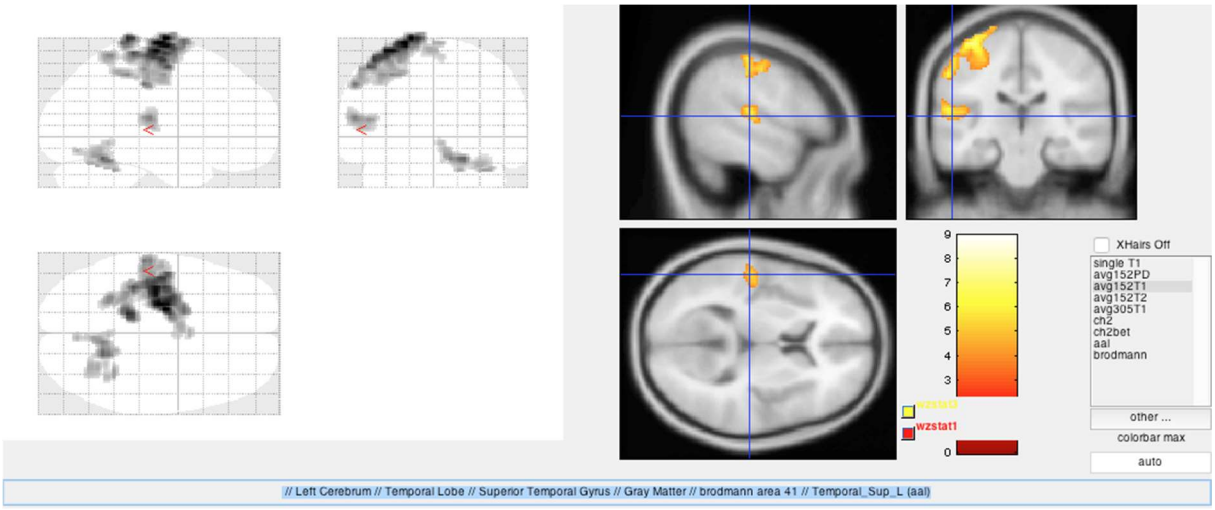

Figure 4.9 Single patient activations for answers that were TRUE. Regions of the figure that appear activated: // Left Cerebrum // Temporal Lobe // Superior Temporal Gyrus // Grey Matter // Brodmann area 41 // Temporal_Sup_L (aal)

In Figure 4.10 it is possible to verify the activation of the Right Temporal Lobe during the response to one of the activities of the paradigm, more specifically during the answers that were FALSE.

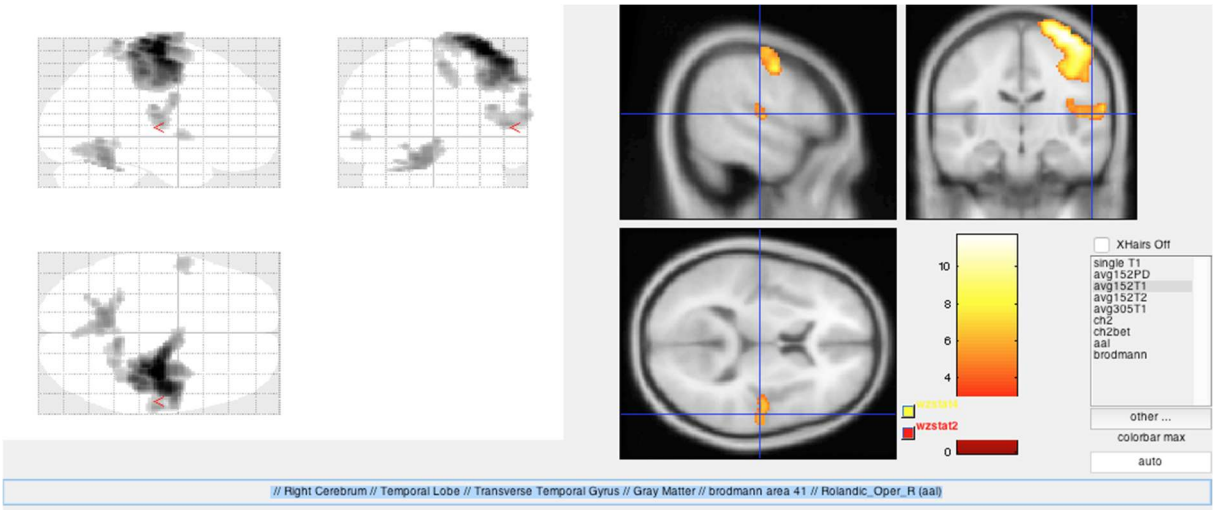

Figure 4.10 Single patient activations for answers that were FALSE. Regions of the figure that appear activated: // Right Cerebrum // Temporal Lobe // Transverse Temporal Gyrus // Grey Matter // Brodmann area 41 // Rolandic_Oper_R (aal)

Through a more exhaustive analysis of the anatomical regions with activation, it was possible to reach the following observations at the level of Lobes, Gyrus and Specific Area Activation per Patient. The analysis was carried out considering the Patients with High Global Score (HGS), Medium Global Score (MGS) and Low Global Score (LGS). Patients with overall correct answers (both for TRUE and FALSE) below 40% of correct answers, were classified as being in the LGS. Patients between 40% and 70% were classified as MGS. And patients with a score of 70% to 100% were classified as patients with HGS.

Thus, it is possible to indicate, according to the stimuli presented during scanning, a classification according to the responses made during the recognition test, where a correct response indicates that the stimulus was subsequently remembered, whereas an incorrect response indicates that the stimulus was subsequently forgotten.

Figure 4.11 indicates how many patients fell into each category. In this case, half of the patients (6) fell in HGS, 2 in MGS, and 4 in LGS.

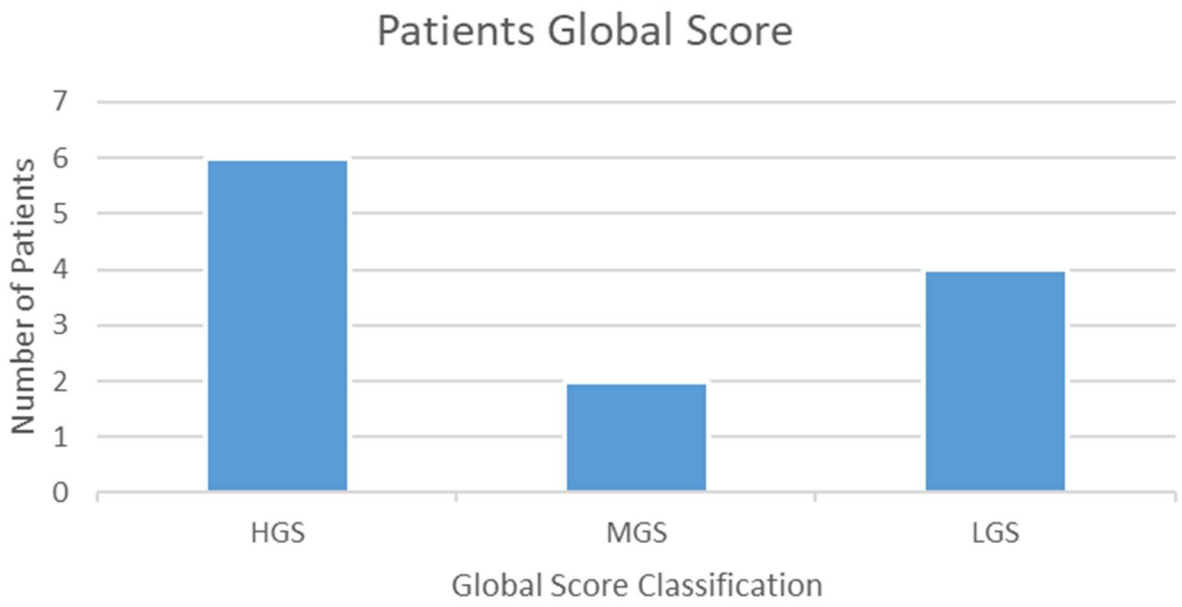

Figure 4.11 Number of patients with High Global Score (HGS), Medium Global Score (MGS) and Low Global Score (LGS). This classification was used in the study of anatomical regions to have a perception of activated regions vs the patients' global score.

Here are the data that had more patients with activation in these regions, but in Annex A all the activated regions are shown. The anatomical regions nomenclature follows the automated anatomical atlas (aal) [88], [89], which is widely used in neuroimaging research.

4.3.2.1. Activated Lobe Regions

For the study and taking into account the answers to TRUE, the activated regions, with regard to the Lobes, were the Temporal Lobe, Cerebellum Posterior Lobe, Frontal Lobe, Limbic Lobe, Occipital Lobe, Parietal Lobe, Sub-lobar, Temporal Lobe, as we can see from Figure 4.12.

The regions with the most activation cases were the Frontal Lobe, Parietal Lobe and Temporal Lobe with 91.67% of cases and the Limbic Lobe had the least activation, with 50% of cases.

In patients with HGS, the regions with the most cases of activation were the Temporal Lobe, Parietal Lobe, Frontal Lobe, and Cerebellum Anterior Lobe with 50% of cases. In patients with MGS + LGS, the regions with the most cases were the Occipital Lobe, Temporal Lobe, Parietal Lobe, and Frontal Lobe with 41.67%.

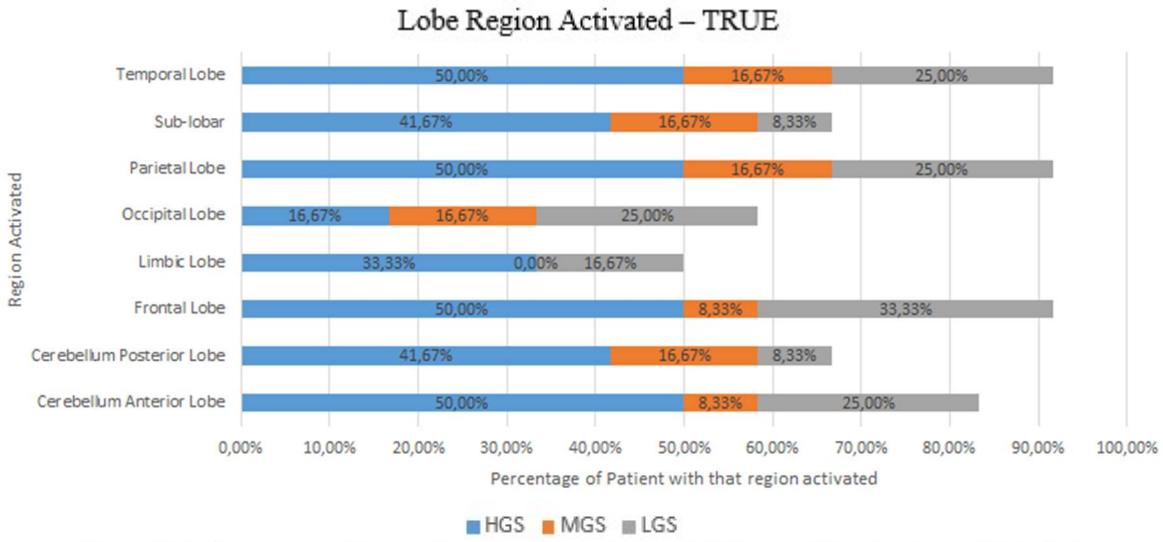

Figure 4.12 Activated regions, with regard to the Lobes in the TRUE part of the paradigm. Patients with High Global Score (HGS) in blue. Patients with Medium Global Score (MGS) in orange. Patients with Low Global Score (LSG) in grey.

To verify if the patients answered correctly in the cases where the answer was FALSE, we can observe that the activated regions Frontal Lobe, Occipital Lobe, Parietal Lobe, Temporal Lobe, Cerebellum Anterior Lobe, Cerebellum Posterior Lobe, Limbic Lobe, and Sub-lobar, as shown in Figure 4.13.

The lobe with the highest percentage of patients with activation was the Frontal Lobe with 91.67%, followed by the Cerebellum Anterior Lobe, Temporal Lobe, and Parietal Lobe with 83.33% of cases respectively.

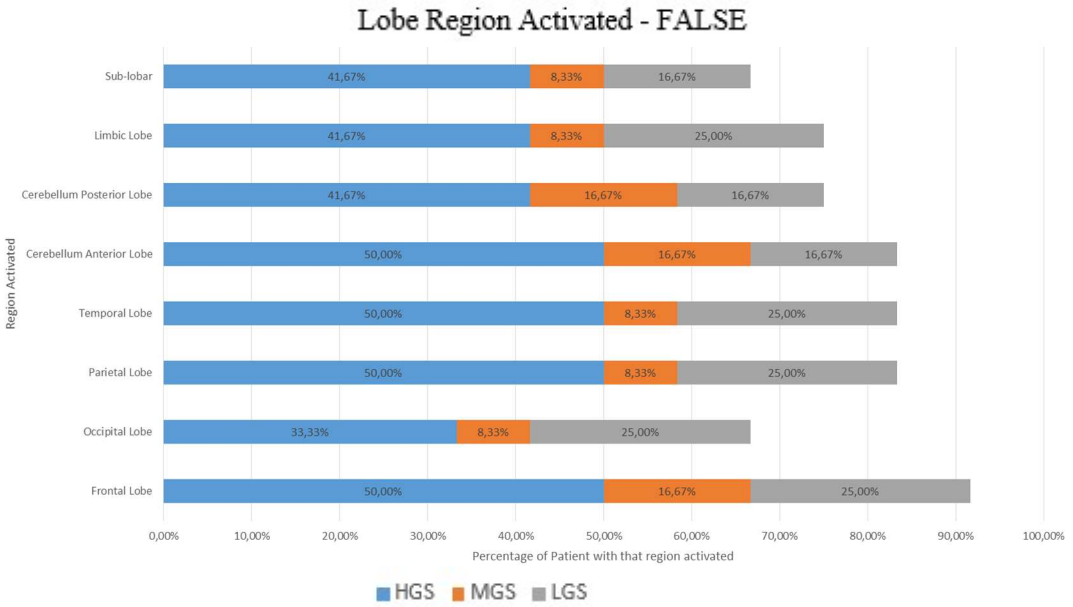

Figure 4.13 Activated regions, with regard to the Lobes in the FALSE part of the paradigm. Patients with High Global Score (HGS) in blue. Patients with Medium Global Score (MGS) in orange. Patients with Low Global Score (LSG) in grey.

4.3.2.2. Activated Gyrus Regions

Going to a more specific areas of the brain, the Gyri, we can observe in Figure 4.14 that the regions with percentages of patients that had more activations for TRUE are the Superior Temporal Gyrus and the Culmen with 83.33% of the cases of which 50% were in patients with HGS, and 25% of cases in patients with LGS. After these regions we can see that the Precentral Gyrus and the Declive were the other regions with the highest percentage of patients with activation reaching 66.67%.

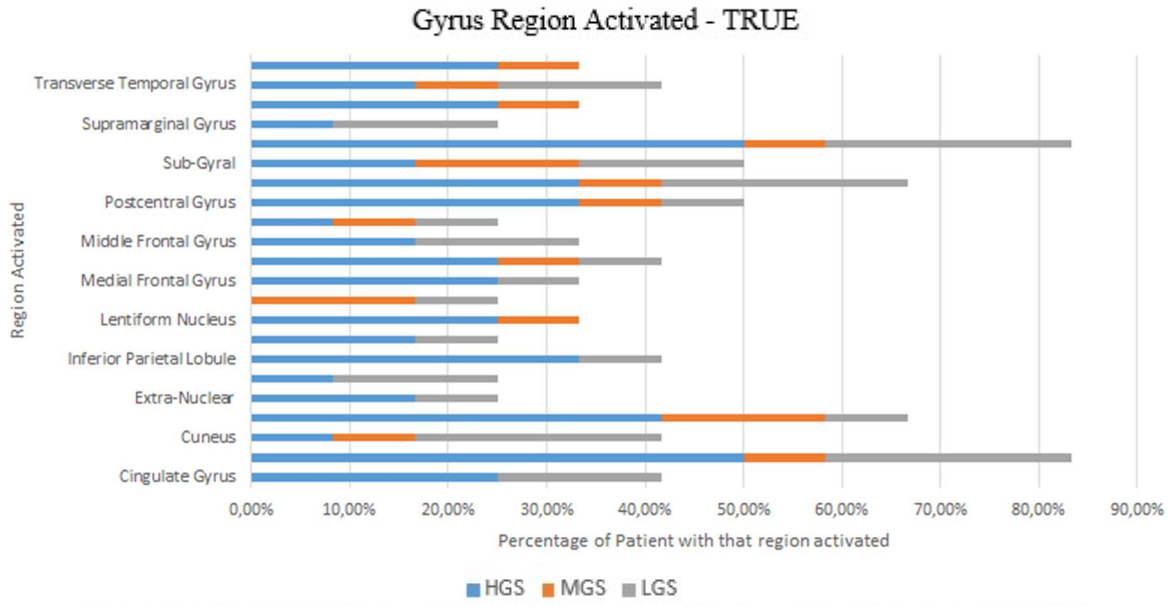

Figure 4.14 Activated regions, with regard to the Gyrus in the TRUE part of the paradigm. Patients with High Global Score (HGS) in blue. Patients with Medium Global Score (MGS) in orange. Patients with Low Global Score (LSG) in grey.

Regarding Gyrus for FALSE, the region with the highest percentage of patients with activation was Culmen with 83.33% of cases, followed by Superior Temporal Gyrus with 75%, Postcentral Gyrus and Declive with 66.67%.

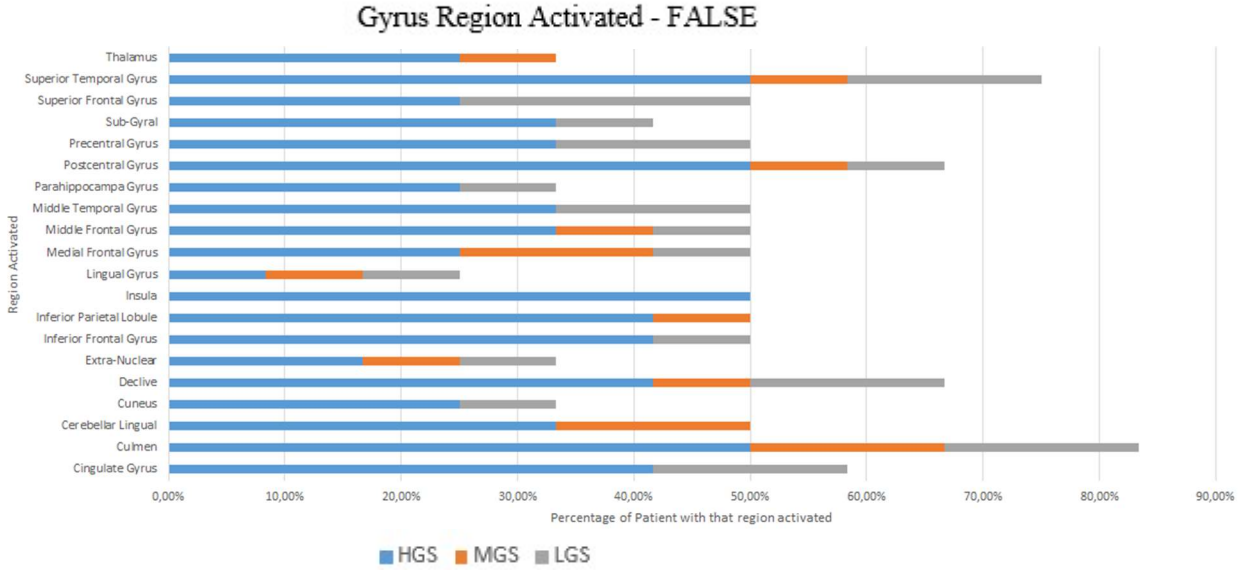

Figure 4.15 Activated regions, with regard to the Gyrus in the FALSE part of the paradigm. Patients with High Global Score (HGS) in blue. Patients with Medium Global Score (MGS) in orange. Patients with Low Global Score (LSG) in grey.

4.3.2.3. Specific Area Activation per Patient

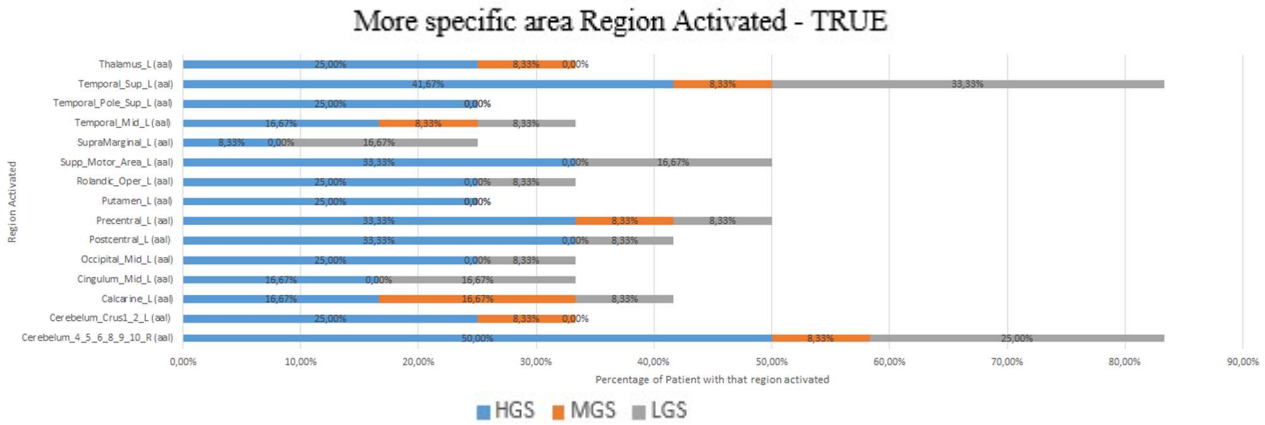

Figure 4.16 Activated regions, with regard to Specific Areas in the TRUE part of the paradigm. Patients with High Global Score (HGS) in blue. Patients with Medium Global Score (MGS) in orange. Patients with Low Global Score (LSG) in grey.

For the more specific areas of the brain, as shown in Figure 4.16, the regions with the highest percentage of patients with TRUE activation were Temporal_Sup_L (aal) and Cerebelum_4_5_6_8_9_10_R (aal) with 83.33% respectively followed by Supp_Motor_Area_L (aal) and Precentral_L (aal) with 50% respectively. Cerebelum_4_5_6_8_9_10_R (aal) is the region with the highest percentage of patients with HGS having 50% of cases and Temporal_Sup_L (aal) is the region with the highest percentage of patients with LGS having 33.33% of cases.

Here, in the more specific regions, a comparative analysis was performed between all patients with HGS (6 patients), MGS (2 patients) and LGS (4 patients) regarding the cases in which the answer should be TRUE.

On the one hand, all patients with HGS, i.e., 100% of patients, had activation in Cerebelum_4_5_6_8_9_10_R (aal) and 50% of MGS and 75% of LGS had activation in the same region. On the other hand, 100% of patients with LGS had activation in Temporal_Sup_L (aal) where a high percentage of activation was observed in patients with HGS, 83.33%, and a percentage of 50% in patients with MGS.

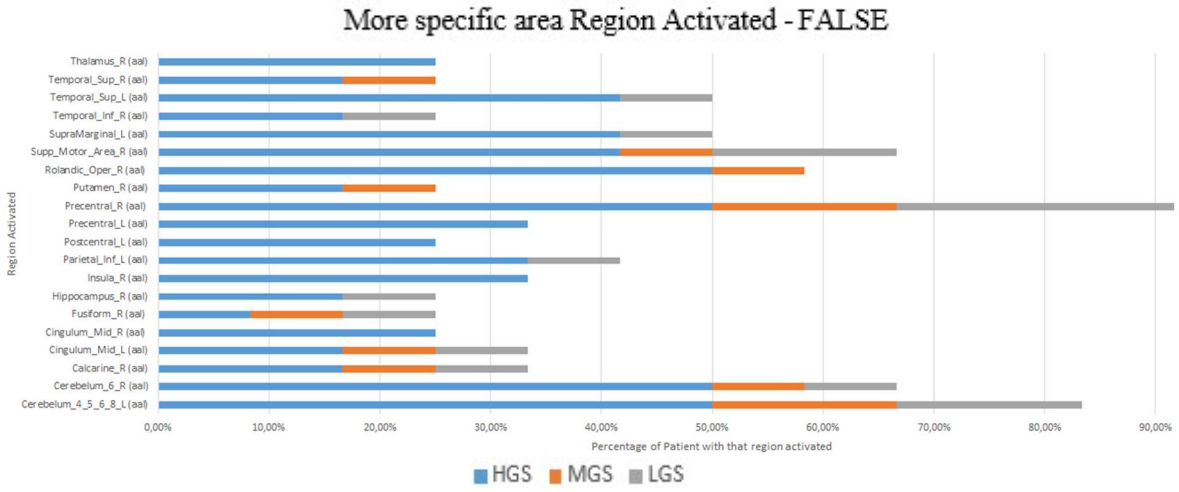

Figure 4.17 Activated regions, with regard to Specific Areas in the FALSE part of the paradigm. Patients with High Global Score (HGS) in blue. Patients with Medium Global Score (MGS) in orange. Patients with Low Global Score (LSG) in grey.

In the more specific regions for FALSE, as can be seen from Figure 4.17, it can be seen that the region that had the highest percentage of patients with activation was Precentral_R (aal) with 91.67% of cases, followed by Cerebelum_4_5_6_8_L (aal) with 83.88% of cases and of Supp_Motor_Area_R (aal) and Cerebelum_6_R (aal) with 66.66% of cases.

Here, in the more specific regions, a comparative analysis was carried out between all patients with HGS (6 patients), MGS (2 patients) and LGS (4 patients) referring to the cases in which the answer should be FALSE.

100% of patients with HGS had activation in Cerebelum_6_R (aal), Cerebelum_4_5_6_8_L (aal), Precentral_R (aal) and Rolandic_Oper_R (aal). In some of these the same was found, 100% of patients with activation, for those who had MGS, namely for the Precentral_R (aal) and for the Cerebelum_4_5_6_8_L (aal). In patients with LGS there were above 50% of patients with activation only in Precentral_R (aal) with 75% of cases.

As mentioned in sub chapter 2.2.2, Mesial Temporal Sclerosis affects usually structures located in the medial and lateral temporal cortex, in particular the hippocampus, parahippocampal gyrus and the amygdala.

We can say that our study corroborates what was found in Holmes et al. 2013 [42]. If we look at Figure 4.12 and Figure 4.13, we can see that the Temporal Lobe is one of those with more patient activation, but in our study, we found that the Frontal Lobe also seems to be activated, which according to some studies [90], [91] plays an important role in human memory.

But we can see in Figure 4.15 to Figure 4.17 that both the hippocampus, and parahippocampal gyrus are areas that have more patients with activation, but here there are other regions that seem to show even more activation, which again may be indicative of the brain's plasticity.

Based on the work of Sidhu et al. 2013 [36], and from what we can see in Table 2.3, patients with Hippocampal Sclerosis showed activation of the posterior hippocampus, parahippocampal gyrus, fusiform gyrus, orbitofrontal cortex and anterior cingulate cortex in the subsequent verbal memory task, and they showed activation of the posterior hippocampus, parahippocampal gyrus, fusiform gyrus, insula, orbitofrontal cortex and amygdala in the subsequent visual memory task.

From our study, the subsequent memory effect is related to the face-name pair. And similarities are found in the activations of the hippocampus, fusiform and insula, mainly in relation to the regions seen in Figure 4.17 (referring to FALSE). And in both Figure 4.16 (referring to TRUE) and Figure 4.17 (referring to FALSE), similarities can be seen in relation to the cingulate. This means that our study agrees with what can be found in the literature and provides some additional information about the regions with activation.

We have found relevant information in the task that relates to motor responses. In this memory paradigm with motor tasks, motor regions were activated as expected, such as Supp_Motor_Area_R, Supp_Motor_Area_L and Precentral Gyrus. The inclusion of a motor response resulted in an overlap of memory responses with motor responses. Which, according to Kinder and Buss 2020 [92], enhances memory encoding.

According to Meule 2017 [93], In most studies, patients are required to respond with a button press to the relevant stimuli, but researchers need to carefully interpret their findings derived from this kind of response particularly when these findings diverge depending on whether using reaction times or accuracy. This means that a paradigm that uses button press can have problems related to reaction time, which in turn can lead to incorrect decisions about whether the answers are correct or incorrect.

As indicated by some studies [94], [95], the interference between two concurrent tasks is associated with activation of overlapping fields in the cortex, because they require activation of overlapping areas of the cerebral cortex. And these same studies indicate that this results in an increase in reaction time, if they require activation of overlapping parts of the cortex.

From Figure 4.8 , regarding the hand grasping paradigm, we have activation of the motor cortex and the auditory cortex. Additionally, activation of the temporal lobe and hippocampus is also observed. From the memory paradigm it is also observed the activation of the temporal lobe which is one of the regions with activation for almost all of the patients, as shown in Figure 4.12 and Figure 4.13.

It is important to highlight that temporal lobe activation in memory is more prevalent than in hand grasping, ending up having a predominant role. In the hand grasping paradigm, there are other areas more predominant than the temporal lobe, such as areas related to the motor cortex and the auditory cortex. For hand grasping, there was observed activation in the brodmann areas in general, something that was not observed in memory. In regions such as Supp_Motor_Area_L (aal) and Supp_Motor_Area_R (aal), Postcentral_L (aal), Postcentral_R (aal), Precentral_L (aal) and Precentral_L (aal) activations were observed for both paradigms.

Unfortunately, our design precludes us from drawing any other inferences as to how motor performance can affect the performance of the memory paradigm. However, the differences between the patients' activation maps in relation to the two paradigms lead us to think that the motor performance did not negatively disturb the memory paradigm, and may even have even improved memory mapping, since it may result in an increase in reaction time [94], [95]. Furthermore, the fact that we can obtain the data shown in the Reference Time Courses (RTCs) evaluation chapter is evidence that the overlapping of motor activation does not overlap with memory activation to the point that we cannot extract the necessary data for the study.

Chapter 5
Conclusions

This study aims to assess the functional network associated with memory in patients with TLE using a memory paradigm involving hand grasping in response to stimuli. To this end, a functional paradigm was designed, and data collection and analysis were performed.

First, a literature review was carried out. In this way it was possible to learn about memory, TLE and the design of paradigms. It was possible to perceive that the design of paradigms has a great influence on the study to be conducted and the results to be obtained. In the study conducted by Buck and Sidhu 2020 [41], they created a guide for the development of an fMRI memory paradigm for pre-surgical evaluation of TLE. In it, they addressed the fact that there is a growing interest in the clinical and experimental application of functional fMRI memory testing. They talked about the technical and methodological considerations to optimise both the sensitivity and specificity of this fMRI modality and provided some recommendations to consider when developing a fMRI memory paradigm, such as paradigms that incorporate encoding and recall.

In this study, we attempted to conduct an empirical work in which the development of a memory paradigm is put to the test and compared with other studies as reported in the literature. Comparisons mainly with paradigms where the response to stimuli is through buttons. Some conclusions were taken from this empirical study.

From the results and the discussion, we have had above, we can conclude that the memory paradigm supported by a motor response leads to good results in terms of responses and robustness of a paradigm that uses the motor response to stimuli.

The hypothesis of whether it is possible to achieve the same level of accuracy with the hand grasping and memory paradigm implemented in this study we consider that we achieved good results based on the number of correct responses obtained, compared to what can be found in the literature about other paradigms, such as paradigms that use buttons to respond to stimuli. However, the hypothesis that a more continuous hand grasping response may end up being more effective than a response given by buttons remains to be verified.

Despite the results obtained in this study, there are some limitations in our methods that should be considered. Our sample size of 12 patients is still relatively small, but this can be considered a pilot study of a relatively homogeneous patient population clinically speaking. With these results, we hope

to stimulate further research in the field of memory network neuroscience in TLE and to extend these results as we add more patients. Future studies could use larger samples and consider age groups.

The fact that we do not have a control group can be seen as another limitation of this study. This means that in future studies with more material conditions, such us buttons to respond to the stimuli, a comparative study between patients responding with hand grasping vs. button can be performed. In order to avoid a learning effect, one could perform hand grasping first and then button response in a certain group and button first and then hand grasping in another group. To draw even more conclusions about memory loss, it would be beneficial to have a group of epilepsy patients and a group of healthy patients perform the same paradigm to see if there is a difference between these two groups, i.e., the regions of activation, the number of correct responses and more generally to see if there is a big difference between a healthy person and a person with epilepsy in terms of memory.

Finally, this study represents only one contribution to the knowledge of functional connectivity of memory in patients with TLE. Given the importance of the topic, it is considered that there is still a long way to go, both in terms of knowledge about TLE, the impact of TLE on memory, and the paradigms that should be considered when designing a memory fMRI paradigm, bearing in mind that there is no single "gold standard" memory fMRI protocol due to the variability of parameters to be considered, such as the stimuli themselves or the paradigm design.

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Annex A

Activated Lobe Regions TRUE

Table A.1 Activated Lobe Regions percentage of patients who correctly responded to the TRUE part of the paradigm (Names and faces that were correct and the patient said they were correct).

Lobe True	**Percentage of Patients with that region activated**	HGS*	MGS**	LGS***
Cerebellum Anterior Lobe	83.33%	50.00%	8.33%	25.00%
Cerebellum Posterior Lobe	66.67%	41.67%	16.67%	8.33%
Frontal Lobe	91.67%	50.00%	8.33%	33.33%
Limbic Lobe	50.00%	33.33%	0.00%	16.67%
Occipital Lobe	58.33%	16.67%	16.67%	25.00%
Parietal Lobe	91.67%	50.00%	16.67%	25.00%
Sub-lobar	66.67%	41.67%	16.67%	8.33%
Temporal Lobe	91.67%	50.00%	16.67%	25.00%

*HGS: High Global Score HGS. ** MGS: Medium Global Score. *** LSG: Low Global Score.

Activated Lobe Regions FALSE

Table A.2 Activated Lobe Regions percentage of patients who correctly responded to the FALSE part of the paradigm (Names and faces that were not a match/incorrect and the patient said they were incorrect).

Lobe False	**Percentage of Patients with that region activated**	HGS*	MGS**	LGS***
Frontal Lobe	91.67%	50.00%	16.67%	25.00%
Occipital Lobe	66.67%	33.33%	8.33%	25.00%
Parietal Lobe	83.33%	50.00%	8.33%	25.00%
Temporal Lobe	83.33%	50.00%	8.33%	25.00%
Cerebellum Anterior Lobe	83.33%	50.00%	16.67%	16.67%
Cerebellum Posterior Lobe	75.00%	41.67%	16.67%	16.67%
Limbic Lobe	75.00%	41.67%	8.33%	25.00%
Sub-lobar	66.67%	41.67%	8.33%	16.67%

*HGS: High Global Score HGS. ** MGS: Medium Global Score. *** LSG: Low Global Score.

Activated Gyrus Regions TRUE

Table A.3 Activated Gyrus Regions percentage of patients who correctly responded to the TRUE part of the paradigm (Names and faces that were correct and the patient said they were correct).

Gyrus True	**Percentage of Patients with that region activated**	HGS*	MGS**	LGS***
Anterior Cingulate	8.33%	8.33%	0.00%	0.00%
Cerebellar Tonsil	8.33%	8.33%	0.00%	0.00%
Cingulate Gyrus	41.67%	25.00%	0.00%	16.67%
Culmen	83.33%	50.00%	8.33%	25.00%
Cuneus	41.67%	8.33%	8.33%	25.00%
Declive	66.67%	41.67%	16.67%	8.33%
Extra-Nuclear	25.00%	16.67%	0.00%	8.33%
Fusiform Gyrus	8.33%	0.00%	8.33%	0.00%
Inferior Frontal Gyrus	25.00%	8.33%	0.00%	16.67%
Inferior Parietal Lobule	41.67%	33.33%	0.00%	8.33%
Inferior Semi-Lunar Lobule	8.33%	8.33%	0.00%	0.00%
Insula	25.00%	16.67%	0.00%	8.33%
Lentiform Nucleus	33.33%	25.00%	8.33%	0.00%
Lingual Gyrus	25.00%	0.00%	16.67%	8.33%
Medial Frontal Gyrus	33.33%	25.00%	0.00%	8.33%
Middle Temporal Gyrus	41.67%	25.00%	8.33%	8.33%
Middle Frontal Gyrus	33.33%	16.67%	0.00%	16.67%
Middle Occipital Gyrus	25.00%	8.33%	8.33%	8.33%
Postcentral Gyrus	50.00%	33.33%	8.33%	8.33%
Posterior Cingulate	16.67%	16.67%	0.00%	0.00%
Precentral Gyrus	66.67%	33.33%	8.33%	25.00%
Precuneus	16.67%	8.33%	0.00%	8.33%
Sub-Gyral	50.00%	16.67%	16.67%	16.67%
Superior Frontal Gyrus	16.67%	16.67%	0.00%	16.67%
Superior Temporal Gyrus	83.33%	50.00%	8.33%	25.00%
Supramarginal Gyrus	25.00%	8.33%	0.00%	16.67%
Thalamus	33.33%	25.00%	8.33%	0.00%
Transverse Temporal Gyrus	25.00%	16.67%	8.33%	16.67%
Tuber	33.33%	25.00%	8.33%	0.00%

*HGS: High Global Score HGS. ** MGS: Medium Global Score. *** LSG: Low Global Score.

Activated Gyrus Regions FALSE

Table A.4 Activated Gyrus Regions percentage of patients who correctly responded to the FALSE part of the paradigm (Names and faces that were not a match/incorrect and the patient said they were incorrect).

Gyrus False	**Percentage of Patients with that region activated**	HGS*	MGS**	LGS***
Cingulate Gyrus	58.33%	41.67%	0.00%	16.67%
Culmen	83.33%	50.00%	16.67%	16.67%
Cerebellar Lingual	50.00%	33.33%	16.67%	0.00%
Cuneus	33.33%	25.00%	0.00%	8.33%
Declive	66.67%	41.67%	8.33%	16.67%
Extra-Nuclear	33.33%	16.67%	8.33%	8.33%
Fusiform Gyrus	8.33%	0.00%	0.00%	8.33%
Inferior Frontal Gyrus	50.00%	41.67%	0.00%	8.33%
Inferior Occipital Gyrus	8.33%	8.33%	0.00%	0.00%
Inferior Parietal Lobule	50.00%	41.67%	8.33%	0.00%
Insula	50.00%	50.00%	0.00%	0.00%
Lateral Ventricle	8.33%	0.00%	0.00%	8.33%
Lentiform Nucleus	8.33%	8.33%	0.00%	0.00%
Lingual Gyrus	25.00%	8.33%	8.33%	8.33%
Medial Frontal Gyrus	50.00%	25.00%	16.67%	8.33%
Middle Frontal Gyrus	50.00%	33.33%	8.33%	8.33%
Middle Occipital Gyrus	8.33%	0.00%	0.00%	8.33%
Middle Temporal Gyrus	50.00%	33.33%	0.00%	16.67%
Parahippocampa Gyrus	33.33%	25.00%	0.00%	8.33%
Postcentral Gyrus	66.67%	50.00%	8.33%	8.33%
Posterior Cingulate	8.33%	0.00%	8.33%	0.00%
Precentral Gyrus	50.00%	33.33%	0.00%	16.67%
Precuneus	16.67%	8.33%	0.00%	8.33%
Pyramis	8.33%	0.00%	8.33%	0.00%
Sub-Gyral	41.67%	33.33%	0.00%	8.33%
Superior Frontal Gyrus	50.00%	25.00%	0.00%	25.00%
Superior Temporal Gyrus	75.00%	50.00%	8.33%	16.67%
Supramarginal Gyrus	16.67%	8.33%	0.00%	8.33%
Thalamus	33.33%	25.00%	8.33%	0.00%
Transverse Temporal Gyrus	16.67%	16.67%	0.00%	0.00%

*HGS: High Global Score HGS. ** MGS: Medium Global Score. *** LSG: Low Global Score.

Specific Area Activation per Patient TRUE

Table A.5 Specific Area Activation per Patient percentage of patients who correctly responded to the TRUE part of the paradigm (Names and faces that were correct and the patient said they were correct).

Specific Area Activation per Patient TRUE	**Percentage of Patients with that region activated**	HGS*	MGS**	LGS***
Cerebelum_4_5_6_8_9_10_R (aal)	83.33%	50.00%	8.33%	25.00%
Cerebelum_6_L (aal)	16.67%	8.33%	8.33%	0.00%
Cerebelum_Crus1_2_L (aal)	33.33%	25.00%	8.33%	0.00%
Cerebelum_Crus1_R (aal)	16.67%	16.67%	0.00%	0.00%
Vermis_6 (aal)	16.67%	8.33%	8.33%	0.00%
Amygdala_R (aal)	8.33%	8.33%	0.00%	0.00%
Angular_L (aal)	8.33%	0.00%	0.00%	8.33%
Calcarine_L (aal)	41.67%	16.67%	16.67%	8.33%
Calcarine_R (aal)	16.67%	8.33%	0.00%	8.33%
Cingulum_Mid_L (aal)	33.33%	16.67%	0.00%	16.67%
Cingulum_Mid_R (aal)	8.33%	8.33%	0.00%	0.00%
Cuneus_L (aal)	8.33%	8.33%	0.00%	0.00%
Frontal_Inf_Oper_L (aal)	8.33%	8.33%	0.00%	0.00%
Frontal_Inf_Orb_R (aal)	8.33%	0.00%	0.00%	8.33%
Frontal_Inf_Tri_L (aal)	8.33%	0.00%	0.00%	8.33%
Frontal_Mid_L (aal)	8.33%	0.00%	0.00%	8.33%
Frontal_Mid_R (aal)	8.33%	8.33%	0.00%	0.00%
Frontal_Sup_L (aal)	16.67%	0.00%	0.00%	16.67%
Frontal_Sup_R (aal)	16.67%	8.33%	0.00%	8.33%
Fusiform_L (aal)	8.33%	0.00%	8.33%	0.00%
Hippocampus_L (aal)	8.33%	0.00%	0.00%	8.33%
Insula_L (aal)	8.33%	0.00%	0.00%	8.33%
Insula_R (aal)	8.33%	8.33%	0.00%	0.00%
Lingual_L (aal)	16.67%	8.33%	8.33%	0.00%
Lingual_R (aal)	8.33%	0.00%	8.33%	0.00%
Occipital_Mid_L (aal)	33.33%	25.00%	0.00%	8.33%
Occipital_Mid_R (aal)	8.33%	0.00%	8.33%	0.00%
Occipital_Sup_L (aal)	16.67%	8.33%	0.00%	8.33%
Occipital_Sup_R (aal)	8.33%	0.00%	0.00%	8.33%
Olfactory_R (aal)	8.33%	8.33%	0.00%	0.00%
Paracentral_Lobule_L (aal)	16.67%	8.33%	0.00%	8.33%
Parietal_Inf_L (aal)	8.33%	0.00%	0.00%	8.33%
Parietal_Sup_L (aal)	16.67%	16.67%	0.00%	0.00%
Parietal_Sup_R (aal)	16.67%	8.33%	0.00%	8.33%
Postcentral_L (aal)	41.67%	33.33%	0.00%	8.33%
Precentral_L (aal)	50.00%	33.33%	8.33%	8.33%
Precentral_R (aal)	16.67%	8.33%	0.00%	8.33%
Precuneus_L (aal)	8.33%	8.33%	0.00%	0.00%
Putamen_L (aal)	25.00%	25.00%	0.00%	0.00%

Putamen_R (aal)	16.67%	8.33%	8.33%	0.00%
Rolandic_Oper_L (aal)	33.33%	25.00%	0.00%	8.33%
Supp_Motor_Area_L (aal)	50.00%	33.33%	0.00%	16.67%
Supp_Motor_Area_R (aal)	8.33%	8.33%	0.00%	0.00%
SupraMarginal_L (aal)	25.00%	8.33%	0.00%	16.67%
SupraMarginal_R (aal)	16.67%	16.67%	0.00%	0.00%
Temporal_Mid_L (aal)	33.33%	16.67%	8.33%	8.33%
Temporal_Mid_R (aal)	16.67%	8.33%	0.00%	8.33%
Temporal_Pole_Sup_L (aal)	25.00%	25.00%	0.00%	0.00%
Temporal_Sup_L (aal)	83.33%	41.67%	8.33%	33.33%
Temporal_Sup_R (aal)	8.33%	8.33%	0.00%	0.00%
Thalamus_L (aal)	33.33%	25.00%	8.33%	0.00%

*HGS: High Global Score HGS. ** MGS: Medium Global Score. *** LSG: Low Global Score.

Specific Area Activation per Patient FALSE

Table A.6 Specific Area Activation per Patient percentage of patients who correctly responded to the FALSE part of the paradigm (Names and faces that were not a match/incorrect and the patient said they were incorrect).

Specific Area Activation Per Patient FALSE	**Percentage of Patients with that region activated**	HGS*	MGS**	LGS***
Cerebelum_4_5_6_8_L (aal)	83.33%	50.00%	16.67%	16.67%
Cerebelum_6_R (aal)	66.67%	50.00%	8.33%	8.33%
Cerebelum_Crus1_L (aal)	16.67%	8.33%	0.00%	8.33%
Cerebelum_Crus1_R (aal)	16.67%	8.33%	8.33%	0.00%
Vermis_4_5_6 (aal)	8.33%	0.00%	8.33%	0.00%
Amygdala_R (aal)	16.67%	8.33%	0.00%	8.33%
Calcarine_L (aal)	16.67%	8.33%	0.00%	8.33%
Calcarine_R (aal)	33.33%	16.67%	8.33%	8.33%
Cingulum_Mid_L (aal)	33.33%	16.67%	8.33%	8.33%
Cingulum_Mid_R (aal)	25.00%	25.00%	0.00%	0.00%
Cuneus_R (aal)	16.67%	8.33%	0.00%	8.33%
Frontal_Inf_Oper_R (aal)	8.33%	8.33%	0.00%	0.00%
Frontal_Inf_Orb_L (aal)	8.33%	8.33%	0.00%	0.00%
Frontal_Inf_Tri_L (aal)	16.67%	16.67%	0.00%	0.00%
Frontal_Mid_L (aal)	16.67%	16.67%	0.00%	0.00%
Frontal_Mid_R (aal)	16.67%	0.00%	8.33%	8.33%
Frontal_Sup_Medial_R (aal)	8.33%	8.33%	0.00%	0.00%
Fusiform_L (aal)	16.67%	8.33%	0.00%	8.33%
Fusiform_R (aal)	25.00%	8.33%	8.33%	8.33%
Heschl_R (aal)	16.67%	16.67%	0.00%	0.00%
Hippocampus_R (aal)	25.00%	16.67%	0.00%	8.33%
Insula_R (aal)	33.33%	33.33%	0.00%	0.00%
Lingual_L (aal)	16.67%	8.33%	8.33%	0.00%
Lingual_R (aal)	8.33%	0.00%	0.00%	8.33%

Occipital_Mid_L (aal)	8.33%	0.00%	0.00%	8.33%
Occipital_Sup_L (aal)	8.33%	0.00%	0.00%	8.33%
Occipital_Sup_R (aal)	16.67%	8.33%	0.00%	8.33%
ParaHippocampal_R (aal)	8.33%	8.33%	0.00%	0.00%
Parietal_Inf_L (aal)	41.67%	33.33%	0.00%	8.33%
Parietal_Inf_R (aal)	8.33%	8.33%	0.00%	0.00%
Parietal_Sup_R (aal)	8.33%	8.33%	0.00%	0.00%
Postcentral_L (aal)	25.00%	25.00%	0.00%	0.00%
Precentral_L (aal)	33.33%	33.33%	0.00%	0.00%
Precentral_R (aal)	91.67%	50.00%	16.67%	25.00%
Putamen_R (aal)	25.00%	16.67%	8.33%	0.00%
Rolandic_Oper_L (aal)	8.33%	8.33%	0.00%	0.00%
Rolandic_Oper_R (aal)	58.33%	50.00%	8.33%	0.00%
Supp_Motor_Area_L (aal)	16.67%	0.00%	8.33%	8.33%
Supp_Motor_Area_R (aal)	66.67%	41.67%	8.33%	16.67%
SupraMarginal_L (aal)	50.00%	41.67%	0.00%	8.33%
SupraMarginal_R (aal)	16.67%	8.33%	8.33%	0.00%
Temporal_Inf_R (aal)	25.00%	16.67%	0.00%	8.33%
Temporal_Mid_L (aal)	16.67%	16.67%	0.00%	0.00%
Temporal_Mid_R (aal)	16.67%	16.67%	0.00%	0.00%
Temporal_Pole_Sup_L (aal)	16.67%	8.33%	0.00%	8.33%
Temporal_Pole_Sup_R (aal)	16.67%	0.00%	8.33%	8.33%
Temporal_Sup_L (aal)	50.00%	41.67%	0.00%	8.33%
Temporal_Sup_R (aal)	25.00%	16.67%	8.33%	0.00%
Thalamus_L (aal)	8.33%	0.00%	8.33%	0.00%
Thalamus_R (aal)	25.00%	25.00%	0.00%	0.00%

*HGS: High Global Score HGS. ** MGS: Medium Global Score. *** LSG: Low Global Score.