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**Interactive cartography of language and memory in patients with focal and pharmaco-resistant epilepsy. Multimodal assessment.**

Sonja Banjac

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## THÈSE

Pour obtenir le grade de

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Présentée par

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Thèse dirigée par **Monica BACIU**, Université Grenoble Alpes

préparée au sein du **Laboratoire Laboratoire de Psychologie et Neuro Cognition**  
dans l'**École Doctorale Ingénierie pour la Santé la Cognition et l'Environnement**

**Cartographie interactive du langage et de la mémoire chez les patients avec épilepsie focale et pharmaco-résistante. Evaluation multimodale**

**Interactive cartography of language and memory in patients with focal and pharmaco-resistant epilepsy. Multimodal assessment.**

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# Abstract

Current theoretical frameworks suggest that human behaviors are based on strong and complex interactions between cognitive processes such as those underlying language and declarative memory that are supported by the interaction between underlying cortical networks. Patients with temporal lobe epilepsy (TLE) present a model for studying the interaction between language and memory since they frequently show difficulties in both domains. The aim of this thesis was twofold. On one side, it aimed at describing language-memory interaction from the fundamental cognitive neuroscience perspective. On the other, it focused on the clinical application of this interactive perspective.

In the present work, we first demonstrate how language and memory can be mapped interactively using a novel fMRI protocol. Using this protocol in healthy individuals, we show that this interaction is based on an extensive fronto-temporo-parietal language and memory network (LMN) including subcortical structures that corresponds well with the network which could be expected based on the existing models. We subsequently explored the reorganization of LMN in left TLE patients using the same protocol. Our results indicated that these patients employ similar LMN, but demonstrate widespread inter- and intra-hemispheric reorganization. They showed reduced activity of regions engaged in the integration and the coordination of the LMN.

Following these results, we explored the functional dynamics of this interactive network. We showed that LMN is dynamic and reconfigures according to task demands and neurological status. By exploring the differences between state-dependent LMN configurations, we identified the key language and declarative memory subprocesses the network is trying to support with its adaptation. On the other hand, studying the reorganization of this reconfiguration in TLE patients allowed us to understand the supplementary processes language-memory interaction needs when the standard interface is not functional.

We conclude our work by proposing a neurocognitive model of language-memory interaction based on the integration of our findings. Moreover, we discuss the importance of exploring this interaction within presurgical evaluation for TLE patients, especially individually. In addition, we present as perspectives of this work the multimodal prediction of postsurgical cognitive outcome in TLE patients. Our work supports the perspective that complex and interactive cognitive functions, such as language and declarative memory, should be investigated dynamically, considering the interaction between cognitive and cortical networks.

**Key words:** Language, Memory, Epilepsy, fMRI, Connectivity, Preoperative assessment

# Résumé

Les cadres théoriques actuels suggèrent que les comportements humains sont basés sur des interactions fortes et complexes entre les processus cognitifs, tels que ceux qui sous-tendent le langage et la mémoire déclarative, et qui reposent sur l'interaction entre les réseaux corticaux sous-jacents. Les patients atteints d'épilepsie du lobe temporal (TLE) constituent un modèle pour l'étude de l'interaction entre le langage et la mémoire puisqu'ils présentent fréquemment des difficultés dans ces deux domaines. L'objectif de cette thèse était double. D'une part, elle visait à décrire l'interaction langage-mémoire du point de vue des neurosciences cognitives fondamentales. D'autre part, elle s'est concentrée sur l'application clinique de cette perspective interactive.

Dans le présent travail, nous démontrons d'abord comment le langage et la mémoire peuvent être cartographiés de manière interactive en utilisant un nouveau protocole d'IRMf (Imagerie par Résonance Magnétique fonctionnelle). En utilisant ce protocole chez des individus sains, nous montrons que cette interaction est basée sur un vaste réseau fronto-temporo-pariétal du langage et de la mémoire (LMN) qui inclut des structures sous-corticales, et qui correspond bien au réseau auquel on pourrait s'attendre sur la base des modèles existants.

Nous avons ensuite exploré la réorganisation du LMN chez des patients TLE gauche en utilisant le même protocole. Nos résultats indiquent que ces patients utilisent un LMN similaire, mais démontrent une réorganisation inter- et intra-hémisphérique étendue. Ils ont présenté une activité réduite des régions engagées dans l'intégration et la coordination du LMN. Suite à ces résultats, nous avons exploré la dynamique fonctionnelle de ce réseau interactif. Nous avons montré que le LMN est dynamique et se reconfigure en fonction des exigences de la tâche et de l'état neurologique. En explorant les différences entre les configurations du LMN dépendant de l'état, nous avons identifié les sous-processus clés du langage et de la mémoire déclarative que le réseau tente de soutenir par son adaptation. D'autre part, l'étude de cette reconfiguration chez les patients TLE nous a permis de comprendre les processus supplémentaires dont l'interaction langage-mémoire a besoin lorsque l'interface standard n'est pas fonctionnelle.

Nous concluons notre travail en proposant un modèle neurocognitif de l'interaction langage-mémoire basé sur l'intégration de nos résultats. De plus, nous discutons de l'importance d'explorer cette interaction dans le cadre de l'évaluation pré-chirurgicale des patients TLE, en particulier au niveau individuel. En outre, nous présentons comme perspectives de ce travail la prédiction multimodale des résultats cognitifs post-chirurgicaux chez les patients TLE. Notre travail soutient la perspective selon laquelle les fonctions cognitives complexes et interactives, telles que le langage et la mémoire déclarative, devraient être étudiées de manière dynamique, en tenant compte de l'interaction entre les réseaux cognitifs et corticaux.

**Mot clés:** Langage, Mémoire, Épilepsie, fMRI, Connectivité, Evaluation préopératoire

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# Preface

This thesis was conducted within the Laboratory of Psychology and Neurocognition (LPNC), University Grenoble Alpes. It was financed and performed within the project REORG (Neurocognitive Reorganization of Language and Memory in patients with temporal lobe epilepsy. An integrative and multidisciplinary approach, ANR-17-CE28-0015-01), and it was also financed by Neurocog (ANR-15-IDEX-02). This project is run by Monica Baciuc (PU-PH, MD). The work presented in this thesis was supported by the other members of the REORG project. Specifically, the MRI acquisitions performed at the Platform IRM 3t IRMaGe of CHU Grenoble-Alpes were supported by Emilie Cousin (IR, Ph.D., LPNC, IRMaGe), Cédric Pichat (IE, LPNC), Johan Pietras (IRMaGe, CHU), Alexander Krainik (PU-PH, MD, IRMaGe, CHU), Laurent Lamalle (Ph.D., IRMaGe, CHU) and Irène Tropès (IRMaGe, CHU). Cédric Pichat provided support for the pretreatment and Emilie Cousin, Monica Baciuc, and Elise Roger (Ph.D., LPNC) for the statistical analyses of the fMRI data. Graph theory analyses were done in consultation with Elise Roger and Cédric Pichat. Anatomical volume analyses were performed by Fabricio Dutra (Ph.D. candidate, LPNC) and Félix Renard (Ph.D.). The hierarchical clustering and the ongoing work regarding the multimodal prediction of surgery outcomes are performed by Laurent Torlay (IE, LPNC). Work with temporal lobe epilepsy patients was supported by Philippe Kahane (PU-PH, MD, CHU) and Lorella Minotti (MD, CHU), and Chrystèle Mosca (Neuropsychologist, CHU) performed the neuropsychological assessment of temporal lobe epilepsy patients.

Patients and healthy participants provided written informed consent for the study that the local ethics committee approved (CPP: N° Id RCB: 2017-A00384-49, local CHUGA number: 38RC17.018; N° Id RCB: 2009-A00362-55, local CHUGA number: 09-CHUG-14). Healthy participants received financial compensation for their participation. Patients were diagnosed with drug-resistant temporal epilepsy and were candidates for curative surgery, and the fMRI evaluations were performed as a part of their presurgical assessment.

This thesis manuscript is composed of five chapters. Chapter 1 presents a theoretical introduction for this work and provides thesis objectives. The following chapters (2, 3, and 4) present the empirical work and are based on the papers which resulted from this thesis. These chapters are generally in the form of articles, although the introduction and discussion sections are extended. The supplementary materials are presented in the respective Appendix. Finally, Chapter 5 presents the general discussion of the presented work and provides perspectives. The main perspectives are illustrated by the preliminary results of the ongoing research work.

Each chapter contains orange boxes summarizing principal conclusions, results, and open questions after each introduction, results, and discussion section. These boxes are intended as an aid through text navigation. In addition, blue boxes named Addendum provide additional information that is not crucial for reading the main text but can help readers unfamiliar with specific topics. Finally, at the end of Chapter 1, a table summarizes the principal ideas

explored within this thesis. This table is again provided at the end of Chapter 5, supplemented by the main conclusions, limitations, and perspectives related to each idea.



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# List of Abbreviations

<b>LMN</b>	Language and Memory Network
<b>TLE</b>	Temporal Lobe Epilepsy
<b>LTLE</b>	Left Temporal Lobe Epilepsy
<b>RTLE</b>	Right Temporal Lobe Epilepsy
<b>HC</b>	Healthy Controls
<b>HS</b>	Hippocampal Sclerosis
<b>ILAE</b>	International League Against Epilepsy
<b>pTri</b>	pars Triangularis
<b>pOp</b>	pars Opercularis
<b>pOrb</b>	pars Orbitalis
<b>SFG</b>	Superior Frontal Gyrus
<b>STG</b>	Superior Temporal Gyrus
<b>MTG</b>	Middle Temporal Gyrus
<b>ITG</b>	Inferior Temporal Gyrus
<b>TPJ</b>	Temporoparietal junction
<b>SMG</b>	Supramarginal Gyrus
<b>AG</b>	Angular Gyrus
<b>p</b>	posterior
<b>m</b>	medial
<b>PM</b>	Posterior Medial network
<b>AT</b>	Anterior-temporal network
<b>RSN</b>	Resting-state Network
<b>DAN</b>	Dorsal Attention Network
<b>FPN</b>	Frontoparietal Network
<b>SAL</b>	Ventral Attention Network (Salience)
<b>LIMB</b>	Limbic Network
<b>DMN</b>	Default Mode network
<b>fMRI</b>	functional Magnetic Resonance Imaging
<b>GE</b>	sentence Generation task
<b>RECO</b>	Recognition task
<b>RA</b>	Recall task
<b>ROI</b>	Region Of Interest
<b>LI</b>	Laterality Index
<b>LH</b>	Left Hemisphere
<b>RH</b>	Right Hemisphere

- *Are you experiencing any problems in your everyday life?*

- *Yes... I am having problems with my memory.*

- *What type of problems?*

- *When I want to say something, I can't find the word...*

*(extract from a conversation with a  
temporal lobe epilepsy patient before fMRI acquisition)*

# Chapter 1

## Theoretical introduction

### Contents

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## 1.1 Knowledge development through interaction

The primary method of reductionism, the dominant approach to science since the 1600s, was to divide a given research problem into as many parts as possible, beginning with the smallest object gradually ascending to the most complex. However, twentieth-century science witnessed limitations of scientific reductionism in explaining complex phenomena (Mitchell, 2009). It became evident that a single discipline cannot fully address complex phenomena that needed an interdisciplinary understanding. One of those integrative fields was cognitive neuroscience, sometimes termed "insalata mista" ("mixed salad") due to its foundation in various disciplines, but primarily representing a result of a "marriage" between fields of psychology and neuroscience (Gazziniga et al., 2014). On the one hand, cognitive psychology is focused on exploring and describing cognitive functions or processes. On the other, the most significant advances in cognitive neuroscience have come from neuroimaging techniques that provided measurement of physiological changes in the human brain during different cognitive processes. The most crucial challenge in this field is reaching a global understanding of the functional organization of the brain (Varoquaux et al., 2018). Just as the field itself was created through the interplay of various fields, today's research within this area tends to explain complex neurocognitive phenomena through interaction.

### 1.1.1 The interactivity of cognitive processes

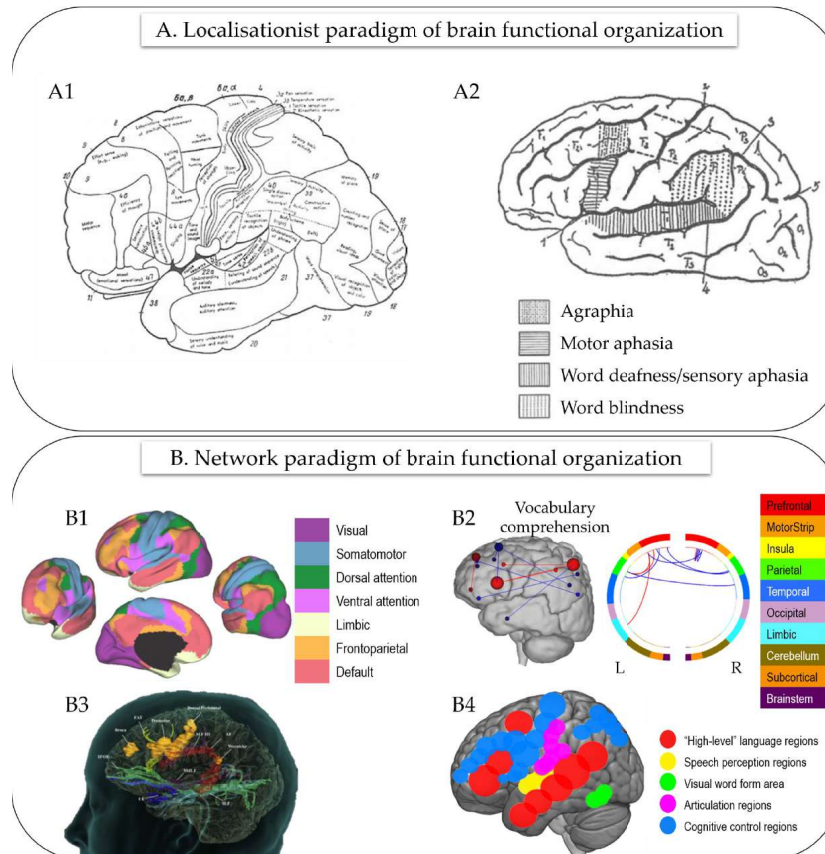
First, even though cognitive processes are defined and delimited for the sake of exploration, everyday behaviors (such as reading this text) engage multiple intertwined processes (Fuster, 2000; Sternberg & Sternberg, 2012). The underlying hypothesis in traditional neuroimaging studies is that it is possible to identify the neural correlates of a specific cognitive process (Poldrack & Yarkoni, 2016). This is usually done using subtraction logic by contrasting the experimental and control conditions that are designed to vary only with respect to the process of interest. However, it is largely acknowledged that this logic is "fragile" when facing real-world psychological tasks. Even standard experimental tasks may recruit processes incidental to task demands. For that reason, it can be hard to specify all cognitive components of a task (Poldrack & Yarkoni, 2016; Price & Friston, 2005; Varoquaux et al., 2018)<sup>1</sup>. Similarly, from a clinical point of view, it is poorly informative to consider a patient's performance on a test in isolation. A cognitive profile can be adequately assessed and comprehended if the entirety of a patient's performance on cognitive tests is considered (Tosi et al., 2020). Moreover, performances on neuropsychological tests are mutually positively correlated since the performance on each test requires a contribution of many processes and can be influenced by other cognitive capacities (Agelink van Rentergem et al., 2020; Holdnack & Drozdick, 2010; Van Der Maas et al., 2006)<sup>2</sup>. During development, skills, and progress

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<sup>1</sup>Price and Friston (2005) give an example of the traditional cognitive model for tool picture naming that includes visual processes, object perception, semantic processing, phonological retrieval, and articulation. However, these authors show that the same task can also implicitly activate "hand movement motor processing" when a picture of a tool is seen.

<sup>2</sup>For instance, performance on verbal working memory tests is influenced by language comprehension and vice versa (Baddeley, 2003), or auditory memory scores can be influenced by language impairments (Holdnack & Drozdick, 2010).

in one domain influence progress in the other domain (Hayne & Simcock, 2008; Houwen et al., 2016; Sundqvist et al., 2016). Therefore, neurocognitive functions do not exist and act in isolation, but in the context of other neurocognitive functions (Boyer, 2010).



**Figure 1.1:** The transition from localisationist to a network-based view of brain organization. (A) Historical examples of localisationist paradigm of brain functional organization. (A1) Detailed map based on symptom-lesion studies of brain-damaged soldiers during WWI proposed by Kleist, figure adapted from Rutten (2017). (A2) Charcot's proposal of localization of aphasias and language centers localization, figure adapted from Rutten (2017). (B) Examples of network paradigm of brain functional organization. (B1) Large-scale cerebral networks proposed by Yeo et al. (2011). (B2) Language network for vocabulary comprehension obtained by Tomasi and Volkow (2020). (B3) Presentation of language-relevant white matter tracts presented by Monroy-Sosa et al. (2021). (B4) Schematic representation of sets of brain regions that are often considered as language network, figure adapted from Fedorenko and Thompson-Schill (2014).

### 1.1.2 The interactivity of cortical systems

Second, decades of neuroimaging research clarified that the brain does not operate in a "one-to-one" fashion (one function - one region). "Single" cognitive process has a distributed activation pattern across different brain regions and the same set of regions can be activated by tasks involving different cognitive processes (Fuster, 2000; Price & Friston, 2005). Also, even when a cognitive function is successfully defined, classified, and experimentally manipulated, it does not imply a separate neural structure. As

we saw, cognitive functions are interdependent and, hence, their neural foundations (Fuster, 2000). Historically, we can separate two schools of thought (see Figure 1.1): (1) anatomical reductionism focusing on the regional localization of cognitive functions (Panel A) and (2) cortical network paradigm (Panel B), proposing that cognitive functions are based on widely distributed cortical systems of interconnected subsystems (Fuster, 2003).

The first perspective is based on the idea that since different cortical areas have different structures, they perform different cognitive functions. This localisationist perspective followed the works of Bouillaud and Broca<sup>3</sup>, among others (Middlebrooks et al., 2017; Rutten, 2017). These findings led to the notion of "eloquent" regions in the context of neurosurgery. Damage or surgery of these eloquent areas highly specialized for a specific function was thought to result in permanent impairments of that function (Duffau, 2018). This localisationist paradigm of inflexible brain functional organization is under question due to methodological drawbacks of the lesional method and the inability to explain functional improvement after resection of "eloquent" regions (Bressler & Menon, 2010; Duffau, 2018). Nevertheless, it should be pointed out that the behavioral-structural lesion method, on which the localisationist paradigm was based, has undergone important progressive changes with the development of imaging techniques and statistical procedures (e.g., Ivanova et al., 2021). Lesion methods have an essential role in cognitive and clinical neurosciences as they provide data distinct from those of other methods and are valuable for causal interferences (Vaidya et al., 2019). Therefore, their advancement is going in the direction of the integration of the network-focused perspectives (Herbet & Duffau, 2020), such as, for instance, "lesion-network-mapping" (Sutterer & Tranel, 2017) and, in general, assimilation with other methods (Vaidya et al., 2019).

The second perspective postulates the existence of specialized areas or modules that are interrelated. Since a collection of specialized brain regions cannot provide a coherent experience, this perspective highlights communication and interaction between and within the modules (Zamora-López et al., 2011). Put differently, higher cognitive functions are based on the interaction of neuronal circuits and brain regions that are supporting various subcomponents of that function (Hagoort, 2016). This holistic concept also mirrors the Gestalt principle - the perception of the entire object emerges from the binding of the parts (Fuster, 2003; Sternberg & Sternberg, 2012). Hence, the organization or the relations between the components are vital for the entity.

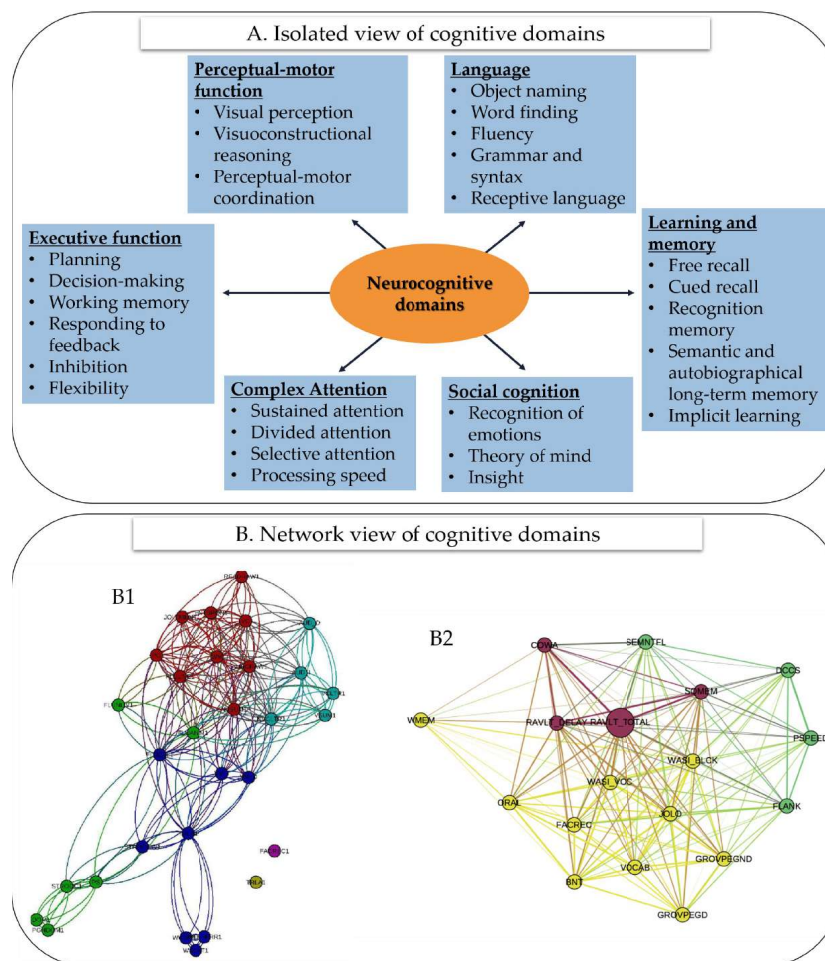
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<sup>3</sup>Two points need to be made here. First, modern neuroscience usually connects the beginning of the cerebral localization theories with 1861 and the observations made by Broca. However, in the opening of the 1861 paper, Broca states that his work supports Bouillaud's ideas and work on locating the lesions associated with speech deficits in the frontal lobes (Rutten, 2017). According to Rutten (2017), the beginning of cerebral localization theories is associated with Broca and not Bouillaud because in 1861, localisationist ideas were more widely accepted than in 1825 (in which Bouillaud published that speech loss corresponds to anterior lobes lesion). Second, even though modern literature still associates Wernicke with localisationist models (e.g., Middlebrooks et al., 2017), he was, in fact, among the first connectionists. Wernicke suggested that the information is distributed across several language centers and that orchestrating multiple areas is necessary for a specific function. His theory on concept acquisition and representation is similar to the contemporary perspective that argues the distribution of the object "knowledge" across brain areas (Gage & Hickok, 2005). This is also supported by the fact that Wernicke never gave a precise anatomical localization of the sensory language areas (Rutten, 2017).

### 1.1.3 Towards cortical and cognitive networks

This network paradigm in cognitive neuroscience emphasized the conjoint functioning of brain regions through the concept of large-scale networks (Panel B, Figure 1.1, Bressler & Menon, 2010). It should be noted that historically network paradigm is rooted in the works of Meynert and Wernicke, among others, who studied the structure and function of the connecting fiber systems (Bressler & Menon, 2010; Monroy-Sosa et al., 2021; Rutten, 2017; Tremblay & Dick, 2016). Moreover, Wernicke proposed a theory on the cortical basis of conceptual knowledge formation and retrieval. He proposed that concepts are widely distributed across the cortex and that transcortical fiber pathways allow linking and binding of these representations (Gage & Hickok, 2005). This network paradigm is also deeply rooted in the work of Mesulam (1990, 1998, 2000), who proposed that neural representation of human behavior is both localized and distributed through multifocal neural systems. These systems can be local, confined to a single cytoarchitectonic field or large-scale networks, composed of widely distributed and interconnected local networks. Mesulam (1990, 2000) proposed that transmodal areas (such as the “Broca’s” and “Wernicke’s” areas for the language network) act as the neural epicenters of these large-scale distributed networks. These multifocal networks have an internal structure that allows complex computations such as parallel distributed processing. Mesulam (1998, 2000) also suggested that cortical areas can dynamically shift affiliation from one network to another according to the task goal. Significant contributions to the development of the network paradigm have also been made by Goldman-Rakic, Bressler, McIntosh, Menon, Fuster, and Sporns, among others. Nevertheless, the comprehensive historical review of the development of this paradigm would surpass the scope of this work (Bressler & Menon, 2010). We will be addressed notion of networks in more detail in Chapter 4.

Notably, the idea of cortical networks from neuroscience echoed in cognitive psychology, firstly through artificial intelligence which gave rise to the idea of parallel distributed processing. The concept of network idea recently gained new interest in the neuropsychological community through the graph theory (see Chapter 4). An increasing number of studies assess dynamic interaction between different cognitive domains using complex neuropsychological assessment in healthy individuals and those with various neurological disorders (Garcia-Ramos et al., 2016; Garcia-Ramos et al., 2021; Kellermann et al., 2016; Tosi et al., 2020). Figure 1.2 illustrates the transition from modular and localisationist towards network perspectives. Cognitive development was similarly proposed to be seen as a web (a concept closely related to the notion of a network) different skills are interacting and integrating, giving rise to complex behaviors (Vallotton & Fischer, 2018).



**Figure 1.2:** The transition from an isolated to a network-based view of cognitive functions. (A) Example of observing cognitive domains (via neurocognitive tests) as isolated and not mutually connected, figure adapted from Sachdev et al. (2014). (B) Examples of exploring interconnections between neurocognitive tests and hence cognitive domains from network perspective, figure B1 adapted from Kellermann et al. (2016), figure B2 adapted from Tomasi and Volkow (2020).

Decades of research are going in the direction of showing that the most plausible cortical and cognitive models have a network structure (Fuster, 2003). The goal of cognitive neuroscience should be to map cognitive networks onto cortical networks since cortical operations occur within and between cortical networks. Beam et al. (2014) performed an interesting semantic analysis of neuroimaging studies revealing the prevalence of single-brain-region terms. These authors predicted that system-level descriptions would gradually replace those terms. The future trend in cognitive neuroscience will be treating information processing as arising from sets of local networks that jointly support complex cognition (Beam et al., 2014).

One of the main focuses of this work is language function and its cerebral representation. However, we saw we cannot explore one cognitive function in isolation. Indeed, in a recent study, Kurashige et al. (2020) found significant evidence on the relationship

between language and other functions. Namely, these authors found that "language", "memory", "concept processing", "executive function", and "self and others" (quotation marks added by the study authors) are intertwined, suggesting that the information processing related to these functions is performed through close interactions between them. Kurashige et al. (2020) also found a densely connected subnetwork mostly related to "concept processing", "action and expression", and "vision and attention" that included perisylvian language networks and left prefrontal cortex structures. This finding suggested an integrated cognitive function that relies on language processing but also depends on functions beyond language processing.

The present work is carried out from the cognitive neuroscientific framework and according to its contemporary network perspective. Therefore, this work will be following two general principles presented in Box 1.1 that sum up previous sections.

The main interest of this study, basing on those grounds, is the interaction between language and memory. Specifically how language relies on memory and how their interaction is reorganized in patients with temporal lobe epilepsy. We will first start by presenting the neurocognitive view of language. In line with the interactive nature of the connection between cognitive functions (Box 1.1), we will point out the close relationship language forms with declarative memory. Following this, we will provide a short neurocognitive overview of memory before discussing the evidence supporting language and declarative memory interaction. Finally, we will explain why patients with temporal lobe epilepsy are the appropriate model for studying this interaction. Figure 1.7 provided at the end of this chapter offers a map showing which chapter will address which topic presented in this introduction.

### Box 1.1 Guiding principles

1. Cognitive processes support everyday behaviors through their interaction and integration.
  2. Cerebral representation of cognitive processes is not organized in "one-to-one" fashion, instead it is a distributed system of brain regions.
- Given these two principles, we can talk about and investigate **cognitive networks** and **cortical networks**.

## 1.2 Language

Language is classically defined as a natural, intrinsic and universal ability of human beings to construct communication systems using codes and to combine these codes in order to exchange information with the others around them (Sternberg & Sternberg, 2012). Language, as a system, has specific properties that are of importance for the present work.

### 1.2.1 Language properties and cognitive organization

First, language is *generative* or *productive* in the sense that, within the limits of its linguistic structure, its users can create a limitless number of new utterances (Hagoort, 2016; Kostić, 2006). Second, language allows us to *dislocate* from time and space and talk about things or events that happened or that will occur in the future, and about hypothetical or imagined events (Kostić, 2006; Sternberg & Sternberg, 2012). Third, language is structured at *multiple levels*. Hence, for describing the cerebral representation of language, the starting point for cognitive neuroscience is usually the cognitive structure of language based on substantial linguistic and psychological knowledge (Small & Hickok, 2015).

Linguistic mental processes can be described through representation levels of mapping sound to meaning (Hickok & Poeppel, 2007). Phonemes, the smallest speech building blocks that have acoustic interpretation are used to construct morphemes, the smallest components that mediate representation of meaning, which are further combined into syntactic constructions. These representations (especially phonemes and morphemes) are in the service of lexical access (Hickok & Poeppel, 2007). Lexical access refers to the process during which the output of perceptual or visual analysis activates word-form representations in the mental lexicon. In addition to phonological, morphological, and syntactic processing, there is also semantic processing that refers to the meaning of words and their relationship. Importantly, here we refer to lexical semantics since the general semantics represents an extensive system that extends into memory systems and other cognitive functions, as we will later see (Binder & Desai, 2011; Hertrich et al., 2020). It should be noted that words are combined via syntactic mechanisms and grammar rules into hierarchical structures that influence their semantic interpretation (Matchin & Wood, 2020). Each aspect of language is a research subject of (psycho)linguistic fields (see Box 1.2). However, language researchers using the term language often refer to various mental processes, and some even argue against sharp boundaries between these linguistic levels (Fedorenko & Thompson-Schill, 2014). For instance, the distinction between mental lexicon and grammar is dissolving. Contemporary linguistic frameworks postulate that the mental lexicon, a mental store of word information, includes semantic information, word forms, and syntactic information (Fedorenko et al., 2020; Gazziniga et al., 2014). Therefore, it should be noted that the division of language processes presented in Box 1.2 is only conditional, and these processes or levels of representation are, in fact, interacting (Kostić, 2006).

**Box 1.2 Main language processes**

Linguistic description	(Psycho)linguistic domain	Level of representation
Speech sounds	Phonology/Phonemics	Phoneme – the smallest distinctive acoustic unit
Word form	Morphology	Morpheme – the smallest meaningful unit of linguistic structure
Word meaning	Semantics	Lexeme – a word created by a combination of phonemes (or morphemes) that has a meaning
Syntactical structures	Syntax	Sentence – a combination of words into larger entities that is governed by grammar rules

Meta-analyses on the neural architecture of presented language processes demonstrated that they rely on an extensive network of distributed regions predominantly set in the left hemisphere with right hemisphere contributions (Price, 2012; Vigneau et al., 2011; Vigneau et al., 2006). However, as Fedorenko and Thompson-Schill (2014) pointed out, to describe language network, one must define what is considered under the term "language" or at least what the language process of interest is. When using the term "language" in this work, we refer to the language used in a natural context. We are particularly interested in the additional cognitive processes that join language to provide everyday communication, especially (as we will later see) memory processes. However, a typical conversation (for instance a chat with a friend) can probably engage majority of cognitive processes and brain networks (Fedorenko & Thompson-Schill, 2014; Hertrich et al., 2020). Thus, we will focus on production rather than language (sentence and narrative) comprehension, even though certain mentioning of language comprehension are necessary. We will begin by describing the cerebral representation of language. We will present the regions that share functional features as a network. Therefore, the term "network" in this manuscript can also be understood as a functional system (Fedorenko & Thompson-Schill, 2014), although we will discuss the structural connections as well.

### 1.2.2 Language network

There are various approaches to describe the language network. We will first present this network based on dual-stream models (for a historical evolution of these models, see Monroy-Sosa et al., 2021) and then based on specific linguistic processes. The two depictions are not mutually exclusive, and they were employed to provide a more comprehensive overview of the neural basis for language.



## Language network through dual stream models

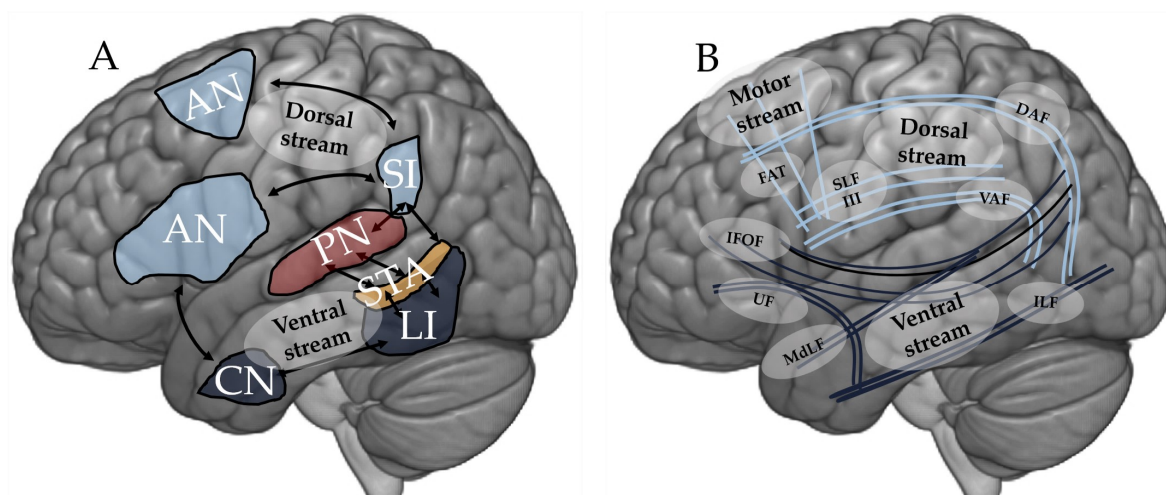
Contemporary language models tend to abandon the traditional modular and serial views of language processing. Instead they propose an extensive language network for semantic, phonological, and syntactic processing based on two pathways organized in parallel and composed of interconnected large-scale, cortico-subcortical sub-networks (Middlebrooks et al., 2017; Monroy-Sosa et al., 2021). Although some dual stream models focus on auditory (e.g., Hickok & Poeppel, 2007) or visual input (e.g., Duffau et al., 2014), they generally agree on the main functional characteristics of the pathways, as well as on the primary fibers they incorporate. The first, **dorsal pathway** is mainly engaged in phonological-motor aspects of speech processing while the other, **ventral pathway**, is involved in lexical-semantic processing (See Figure 1.3, Dick et al., 2014; Duffau et al., 2014; Fridriksson et al., 2016; Herbet & Duffau, 2020; Hickok & Poeppel, 2007).

The historical "Broca–Wernicke–Lichtheim–Geschwind" model was the first to propose **the dorsal stream** but in a simplified way with arcuate fasciculus (AF) connecting inferior frontal ("Broca's") and posterior temporal ("Wernicke's") region (Monroy-Sosa et al., 2021; Tremblay & Dick, 2016). Later studies using modern techniques showed that this stream has a more complex structure. It includes AF and superior longitudinal fasciculus (SLF), connecting regions in the frontal cortex to various regions in the temporal and parietal cortex (Dick et al., 2014; Hertrich et al., 2020; Hickok & Poeppel, 2007; Thiebaut de Schotten et al., 2012). The dorsal stream is sometimes termed the "how" system since it maps perceptual representations of vocal sounds into phonetic, articulatory, syntactic, and motor representations (Hickok & Poeppel, 2007; Ries et al., 2019). This stream also supports the phonological loop or auditory-verbal short-term memory and auditory feedback control during speech production (Hickok, 2012), and it also facilitates speech perception (Kemmerer, 2015).

The **ventral stream** includes uncinata fasciculus (UF) connecting frontotemporal regions, and middle longitudinal fasciculus (mdLF) connecting the caudal and inferior parietal lobule with the superior temporal lobe. It also includes inferior longitudinal (ILF) and inferior frontal-occipital fascicles (IFOF) connecting the occipital lobe with the anterior temporal and the frontal lobes, respectively (Dick et al., 2014; Duffau et al., 2014; Monroy-Sosa et al., 2021). That way, the ventral pathway creates a link between the temporal lobe and various lexical-semantic representations with the inferior frontal lobe regions. Interestingly, the left inferior gyrus was found to show a modular structure corresponding to language processes we discussed, namely phonology, syntax, and semantics. This is evidenced in its connectivity pattern with the temporal lobe for these functions (Hertrich et al., 2020). The ventral stream is sometimes also called the "what" stream since it is engaged in mapping the sound structure of words onto the corresponding semantic representations and in forming the integrated meaning from complex constructions such as phrases and sentences (Kemmerer, 2015).

There are also propositions and evidence that dorsal pathways are involved in organizing elements in sequences (important for sentence generation), while ventral pathways get engaged in the processing of meaning dependencies (Ries et al., 2019). It should be noted that the differences in functional roles of dorsal and ventral pathways are sometimes seen in terms of production vs. comprehension (Kemmerer, 2015), but some authors propose to observe this difference instead in terms of form to articulation vs.

form to meaning (Fridriksson et al., 2016). Indeed, dual stream models have been focused on language perception (or picture naming in the case of Duffau et al., 2014), but others also discussed language production within dual stream framework (e.g., Fridriksson et al., 2016; Hickok, 2012). Generally, these models argue that the dorsal stream engages in speech repetition and auditory feedback control, while the ventral stream is involved in conceptual-to-lexical mapping during production in a similar way to speech perception. It should be noted that dual stream models address functional connectivity between the regions through the notion of streams. However, the dorsal and ventral streams should not be seen as distinct and separated. It is their interconnection that supports language production and comprehension through a variety of linguistic operations (Hickok & Poeppel, 2007; Monroy-Sosa et al., 2021; Silbert et al., 2014).



**Figure 1.3:** Dual stream model of language. (A) Dual stream model proposed by Hickok and Poeppel (2007). The dorsal stream is presented in light blue, and it includes the articulatory network (AN) and the sensorimotor interface (SI). The ventral stream is shown in dark blue, and it is composed of the combinatorial network (CN) and the lexical interface (LI). The dorsal superior temporal gyrus in red is engaged in spectrotemporal analysis (STA), while mid-posterior superior temporal sulcus in yellow is a part of phonological network (PN). The figure is adapted from Monroy-Sosa et al. (2021). (B) White matter within dual stream model. The dorsal stream (light blue) incorporates dorsal and ventral AF (DAF, VAF), SLF, while the ventral stream (dark blue) includes IFOF, UF, ILF, and mLFL. The motor stream consists of the frontal aslant tract (FAT). The figure is adapted from Monroy-Sosa et al. (2021).

### Language network through language processes

Another way of describing language network is through language processes (see Figure 1.4). In doing so, we will follow the previously presented conditional division of language processes and representations (see Box 1.2).

The **phonological subnetwork** is composed of pars opercularis (pOp), supramarginal gyrus (SMG), and mid-to-posterior superior temporal gyrus (STG) (see Figure 1.4,

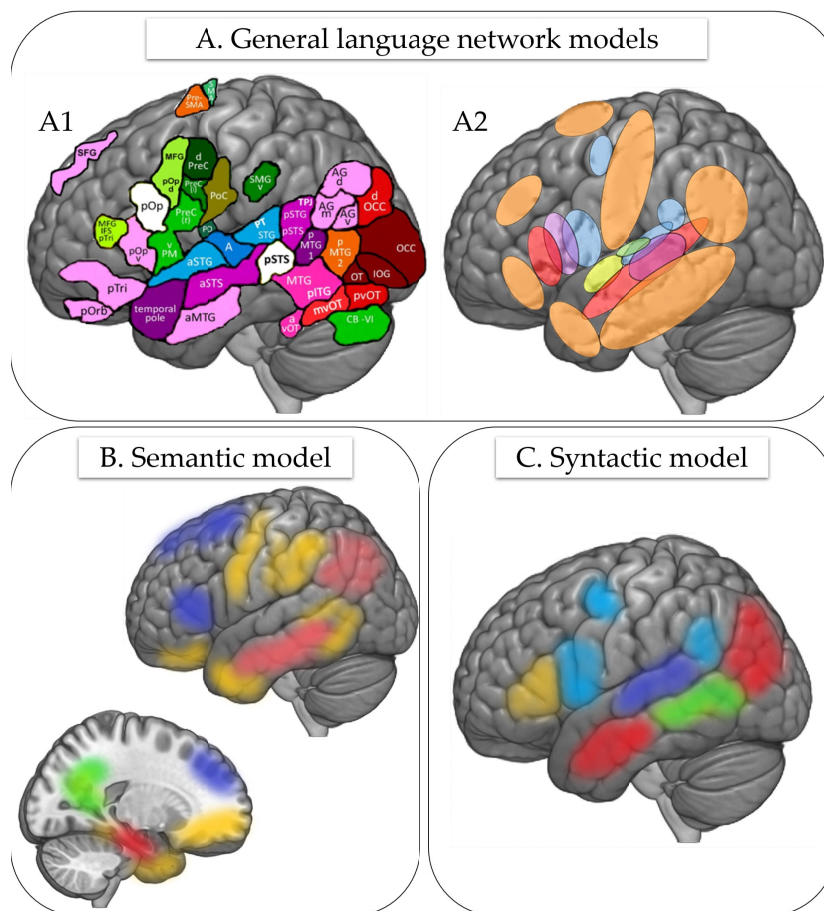
Panel A, Middlebrooks et al., 2017; Price, 2012). Based on their meta-analysis results, Vigneau et al. (2006) propose that this network is organized in two components: a frontal-temporal auditory-motor speech coordination network<sup>4</sup> and a frontal-parietal loop for phonological working memory. The pSTG part of this auditory-phonological network also engages in speech production by providing sound targets for motor-phonological speech planning for sensorimotor network engaged in articulation (Matchin & Hickok, 2020). Regions forming an articulation subnetwork are precentral gyrus, specifically ventral premotor cortex (vPMC), ventral sensorimotor cortex (vSMC), supplementary motor area (SMA), ventral part of SMG, and the posterior end of the Sylvian fissure, Sylvian parietal-temporal junction, that engages in auditory-motor integration (Matchin & Hickok, 2020; Middlebrooks et al., 2017; Price, 2012). Therefore, phonological networks can be seen as asymmetrical regarding the process in question since regions forming the sensory part of the network engage in perception and production, while regions in the motor part of the network engage primarily in speech production (Matchin & Hickok, 2020).

The **semantic network** is distributed across dorsolateral and dorsomedial prefrontal cortex (dlPFC, dmPFC), specifically superior frontal gyrus (SFG), posterior middle frontal gyrus (MFC), dorsal premotor cortex (dPMC), pars orbitalis (pOrb), pars triangularis (pTri), angular gyrus (AG), middle temporal gyrus (MTG), temporal pole (TP), temporoparietal junction (TPJ), the inferior temporal gyrus (ITG), fusiform and posterior cingulate gyrus (see Figure 1.4, especially Panel B, Binder & Desai, 2011; Binder et al., 2009; Cousin et al., 2007; Middlebrooks et al., 2017; Price, 2012; Yvert et al., 2012). Modality-specific sensory, action, and emotion input is sent to high-level convergence zones in temporal and inferior parietal regions, specifically inferior parietal cortex, TPJ, middle and inferior temporal gyri, and the fusiform gyrus (Binder & Desai, 2011). These zones bind representations from different modalities and support abstract representations of entities or objects (anterior STS/MTG) and events or thematic relation between them (AG) (Binder & Desai, 2011). It should be noted that according to some researchers (Duffau et al., 2014; Patterson et al., 2007; Ralph et al., 2017), the temporal pole is the center allowing multimodal integration<sup>5</sup>. Other researchers (Binder & Desai, 2011) see it more as a region that enables emotional and social concepts processing due to its connection with the ventral frontal region and amygdala. Dorsolateral, dorsomedial, and inferior prefrontal cortices are proposed to be engaged in top-down selection and activation of semantic representations by translating affective drive or task goals into a coordinated plan (Binder & Desai, 2011).

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<sup>4</sup>According to Vigneau et al. (2006) meta-analysis, this auditory-motor network is engaged in sensory-motor control (frontal areas, upper motor area for mouth movement, and lower premotor area in precentral gyrus for pharynx and tongue movement) and sensory-motor integration (Rolandic operculum).

<sup>5</sup>Although in the hub-and-spoke models (Patterson et al., 2007; Ralph et al., 2017), the authors refer to the anterior temporal lobe as the amodal hub for semantic generalization (that temporal pole is just a part of). In the original version of this model (Patterson et al., 2007), anterior temporal was seen as a hub engaged in semantic processing regardless of the input modality. In the updated version of this model (Ralph et al., 2017), the authors propose that the anterior temporal lobe shows graded functional specialization, which reflects the differences in the connectivity of the subregions of this hub to the rest of the network.



**Figure 1.4:** Language network and subnetworks models. This figure presents the regions engaged in different language processes. However, what distinguishes them from the localisationist models (presented in Panel A of Figure 1.1) is that they all propose (bidirectional) connections and communication between the presented regions through which the functioning is realized. The regions in all the models are only presented schematically, and their position in the images does not fully correspond to their precise anatomical location. (A) Comprehensive models of language network that include several processes. (A1) Model proposed by Price (2012) based on a meta-analytic view. Blue = auditory processing, dark green = articulation, light green = word retrieval, rose to pink = lexical-semantic processes, dark purple = syntax, red = visual processes, and orange = general action. (A2) The model of core language network and its margins proposed by Hertrich et al. (2020). Green = the auditory cortex, yellow = the auditory word form area, blue = phonological processing, purple = syntax processing, red = lexical-semantic processing, orange = the margins of language network involved in motor activity, cognitive control, emotion processing, etc. (B, C) Example of models focusing on a specific process. (B) The model of semantic processing proposed by Binder and Desai (2011). Yellow = parts of modality-specific sensory, action, and emotion systems, red = high-level convergence zones, blue = cognitive control by goal-directed activation and selection of the information, green = the interface between semantic and hippocampal memory system. (C) The model of cortical organization of syntax proposed by (Matchin & Hickok, 2020). Dark blue = phonological auditory processing, light blue = phonological articulatory processing, green = lexical-syntactic processes, yellow = morpho-syntactic processes, red = conceptual-semantic processing.

It was proposed that pTri is one of the links between semantic and phonological networks since its anterior portion is more involved in semantic function while its posterior portion borders with pOp engaged in phonologic processing (Middlebrooks et al., 2017; Vigneau et al., 2006). Binder and Desai (2011) propose posterior cingulate gyrus and precuneus<sup>6</sup> as an interface between this semantic network and hippocampal memory system that we will describe later on. Through this connection, events that are being encoded in the long-term memory are given meaning.

Regarding *syntactic processing*, there is a growing body of evidence suggesting a substantial integration between it and lexical-semantic processes and representations (see Figure 1.4, especially Panel C, Fedorenko et al., 2020; Matchin & Hickok, 2020). This integration can also be evidenced through their cerebral network overlap (Vigneau et al., 2006). Some even argue against regional specialization in syntactic over lexico-semantic processing (Fedorenko et al., 2020). Even though regions that are proposed to support syntactic processing differ across studies (Haller et al., 2005; Pallier et al., 2011; Segaert et al., 2012), the two primary candidates are posterior inferior frontal gyrus (pOp and pTri) and posterior (medial) temporal gyrus. Indeed, the posterior temporal lobe is engaged both in syntactic, but also lexico-semantic processing (Fedorenko et al., 2020; Hickok & Poeppel, 2007), and in the latest proposal of syntactic cortical organization, Matchin and Hickok (2020) acknowledge that mental lexicon and syntactic rules pertain to the same representational system. Additionally, there is a question of a joint syntactic neural basis for both sentence comprehension and production. Whereas some authors argue in favor of the common implication of pIFG and pMTG (Segaert et al., 2012; Takashima et al., 2020), increasing evidence suggests functional dissociation between these regions. Some studies report that both left pIFG and left pMTG engage in production, but that only pMTG gets involved in perception (Matchin & Hickok, 2020; Matchin & Wood, 2020).

Presented language networks mainly focused on cerebral regions and underlying white matter fibers; nevertheless, subcortical structures also support language functioning. Addendum 1.1 provides more information about main subcortical contributions to language.

## Language network lateralization

We mentioned that language network is predominantly left-lateralized but that right hemisphere is also be involved (Vigneau et al., 2011). The studies on hemispheric lateralization have shown that multiple factors determine the unequal engagement of the hemispheres in different cognitive functions and that lateralization is not homogeneous within the language network (Bradshaw, Bishop, et al., 2017; Josse & Tzourio-Mazoyer, 2004). One of such factors is handedness. Namely, Mazoyer et al. (2014) identified three lateralization types based on manual preference and language lateralization during lexico-semantic and syntactic processing – typical with left hemisphere (LH) dominance (there were 88% of right-handed and 78% of left-handed), ambilateral with no dominant hemisphere (0, 12% of right-handed, 15% of left-handed) and

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<sup>6</sup>In their 2009 meta-analysis, Binder et al. also include parahippocampal gyrus among these semantic-episodic interface regions. However, Binder and Desai (2011) later omit this region when presenting the neuroanatomical semantic processing model.

strongly atypical with right hemisphere (RH) dominance (7% of left-handed). The degree of hemispheric lateralization can also depend on the task (Bradshaw, Bishop, et al., 2017; Tailby et al., 2017). The verbal fluency tasks are considered the golden standard for measuring lateralization in fMRI studies. However, while phonemic fluency and verb generation tasks elicit the strongest lateralization in frontal regions, semantic fluency task has this effect in temporoparietal regions (Bradshaw, Thompson, et al., 2017). Studies also suggest that lateralization conclusions should be based on the regional level since regional heterogeneity or crossed dominance may lead to false conclusions (Bradshaw, Bishop, et al., 2017; Tailby et al., 2017). Moreover, lexico-semantic processing is proposed to be a bilateral process (Hickok & Poeppel, 2007). Binder et al. 2009 meta-analysis of semantic system found that this system is left-lateralized, although the representations in the AG and posterior cingulate gyrus are bilateral. Rice et al. (2015) focused on the anterior frontal lobes and found that conceptual knowledge is represented bilaterally in these regions, although the activations are more likely to be left-lateralized if the semantic concept is accessed linguistically. Indeed, in a meta-analysis of language studies, Vigneau et al. (2011) found limited right hemisphere involvement during processes demanding semantic representations access. These authors also found that the right hemisphere engages less in phonological representations while it is implicated in context processing. The right frontal areas support executive functions (manipulations in working memory) that are not language-specific.

This overview of language function showed us that the language system is highly complex. However, according to contemporary perspectives and the first guiding principle of this thesis (see Box 1.1), no matter how complex a system is, it interacts with others. The other brain regions or pathways do not need to be specialized for language (as are the regions within the core language network), but they are essential for efficient language functioning (Hagoort, 2016; Hertrich et al., 2020). Indeed, some of the presented language models incorporate points or pathways through which language associates with working or long-term memory (Binder & Desai, 2011; Duffau et al., 2014; Hertrich et al., 2020). In addition, a recent study examining the factor structure of cognitive functioning in healthy individuals found that word fluency correlated the most with long-term memory encoding and retrieval (more than working memory and slightly more than acquired knowledge) (Agelink van Rentergem et al., 2020). Finally, Tulving said that semantic memory, part of declarative memory, is "necessary for the use of language" (Tulving, 1972, p. 386). Hence, there is a need to understand why language is so intimately related to memory.

### Addendum 1.1 Subcortical contributions to language networks

Recent neurocognitive language models acknowledge engagement of subcortical structures in higher-order language processing (Duffau et al., 2014; Grandchamp et al., 2019; Hertrich et al., 2020; Løevenbruck et al., 2018; Price, 2012) such as the basal ganglia (Santi et al., 2015; Viñas-Guasch & Wu, 2017), the thalamus (Crosson, 2013) and the cerebellum (Grandchamp et al., 2019; Løevenbruck et al., 2018). Research of linguistic implication of basal ganglia suggests that this structure engages mainly in complex discourse- or syntax-level computation, probably through sequencing (Hertrich et al., 2020; Santi et al., 2015). The putamen is connecting the basal ganglia with language regions. Specifically, its left anterior portion engages in semantic retrieval and comprehension, while the left posterior engages in grammatical and more exhaustive semantic processing (Viñas-Guasch & Wu, 2017).

Thalamus is involved in language processing as a manager of language cortical activities by directing sensory input signals to modality-specific task-relevant regions, connecting basal ganglia and cerebellum with the rest of the cortex, and controlling cortico-cortical connectivity for information flow (for a review of thalamic implication in language processing, see Crosson, 2013; Klostermann et al., 2013). However, in addition to transferring information, the thalamus also has a more complex, integrative role in shaping mental representations (Wolff & Vann, 2019).

The cerebellum plays a role in various language processes, beyond motor aspects of language production (Mariën et al., 2014), both in perceptive and expressive language (Keren-Happuch et al., 2014). It was found to be engaged in phonetic timing operations, segregation of auditory signal, cross-modal binding, and sequencing in verbal fluency (for a complete review, see Mariën et al., 2014). A recent study even highlighted cerebellar implications in semantic integration (Gatti et al., 2020). Regions of the cerebellum that get consistently activated across various language tasks are lobules VI and VII together with Crus I and Crus II (Keren-Happuch et al., 2014; Stoodley & Schmahmann, 2009, 2018). These language activation patterns are more strongly right-lateralized due to the contralateral connection between the left cerebral cortex and right cerebellum (Stoodley & Schmahmann, 2018). Nevertheless, language activation in the level of lobule VI are found to be bilateral (Keren-Happuch et al., 2014; Stoodley & Schmahmann, 2009).

## 1.3 Why would language require memory?

The first obvious answer would be that consistent to the communicative function of language (Kostić, 2006; Sternberg & Sternberg, 2012). Given that language is used to transfer a message, it needs content, which memory can provide. Indeed, researchers like Corballis (2019) proposed that language evolved to allow us to share our mental travels, or to transfer information about an absent action (Von Heiseler, 2014). In that sense, mental time travel (accommodated by episodic memory) is seen as a precursor of language. For some, the reason for this information transmission was a reproductive advantage for the narrator (Von Heiseler, 2014), while others see it in the context

of cooperation (Tomasello, 2009, 2010). Specifically, Tomasello (2010) suggests that communication, in general, represents biological adaptation for collaboration. According to him, arbitrary linguistic conventions develop through shared activities based on joint goals, mutual knowledge, and shared beliefs (all for which long-term memory is necessary). Furthermore, the evolutionary changes in human cognition are thought to have happened as fast as they did, as we were able to transfer the existing knowledge and skills to the members of our species (Tomasello, 2009, 2010).

On the other hand, everyday communication places high demands on language that it cannot answer without other systems (Duff & Brown-Schmidt, 2012; Hertrich et al., 2020). For instance, there is usually a rapid exchange of various messages formulated in multi-modal contexts during a conversation. We are taking into account multiple sources of information at the same time. Also, to understand the information we are receiving and to formulate our message, we rely on our previous memories, knowledge, and beliefs (Duff & Brown-Schmidt, 2012). In general, the key characteristics of language such as being generative or combinatorial, and allowing to dislocate, require the support of other systems, such as memory, among others.

Before presenting in more detail the evidence of interaction between language and memory, we will provide a short overview of memory as a cognitive and neural system and explain what will be considered under the term memory in this work. It should be highlighted that we focus on the language function and how it interacts with other functions, particularly memory. Our interest in memory is only in terms of its interaction with language. Hence, the forthcoming overview of the memory system will not be as elaborated as the presentation of language. It should only provide sufficient information to address our primary focus - how language interacts with memory.

### 1.3.1 A short neurocognitive overview of memory system

In addition to complex language system, humans are also marked by their ability to travel to the past or future mentally. This is mainly achieved through memory processes that store, maintain and retrieve our past experiences to use that information in the present (Sternberg & Sternberg, 2012). This capacity helps us make sense of our lives and create the story that we will communicate.

Memory can be classified as sensory, short-term, and long-term (See Box 1.3). Three main memory processes are encoding, storage and retrieval. Retrieval of information from the long-term memory can occur through the recall process during which a memory item is produced or through a recognition process that allows identifying an item as being seen or heard before (Sternberg & Sternberg, 2012).

We are specifically interested in long-term memory. However, the relation between language and long-term memory cannot be addressed without also considering the information processing performed by working memory. Namely, working memory keeps and moves in and out of temporary memory storage the most recently activated information from long-term memory. The most prevailing model of working memory is the one proposed by Baddeley (Baddeley, 2003; Repovš & Baddeley, 2006; Sternberg & Sternberg, 2012) that is composed of the following elements (see Box 1.3): (1) visuospatial sketchpad that briefly guards visual images; (2) the phonological loop that briefly holds auditory information for verbal comprehension and acoustic rehearsal;



(3) the central executive that manages attentional resources; (4) supplementary “slave systems” that perform other cognitive tasks; (5) the episodic buffer that binds information from the visuospatial sketchpad and phonological loop together with information from long-term memory into a representation. Its relationship with language is widely acknowledged and studied (for overviews, see Baddeley, 2003; Ishkhanyan et al., 2019). Long-term memory can be classified as implicit or non-declarative and explicit or declarative (Squire, 2004). It allows the encoding of memories through relationships between numerous entities and events. The flexibility of this memory supports the adaptation of the performance to different goals. Moreover, declarative memory is representational, and it also provides means to model the external world (Squire, 2004). Ever since Endel Tulving’s work in 1972, declarative memory has been seen through terms (or opposition) semantic-episodic memory, although their conceptualization and the conceptualization of their relationship have changed since then (Renoult & Rugg, 2020).

**Semantic memory** refers to the repository of the general world and conceptual knowledge. It is thought to encompass "encyclopedic" knowledge, schematized representations of events, and personal semantics (i.e., individuals’ conceptual knowledge about themselves) (Renoult et al., 2019). From a memory perspective, semantic memory is most closely related to semantics previously presented in the language system overview (see section 1.2.1). Indeed, Tulving defined it as the memory necessary for language usage. However, he later proposed that not all semantic knowledge is acquired through language (Renoult & Rugg, 2020).

The **episodic memory** system is a dynamic system that engages in reconstructive and combinational processes allowing recollection of past and simulation of future events (Duff et al., 2020; Irish & Piguet, 2013). According to the constructive episodic simulation hypothesis (Schacter & Addis, 2007), episodic memory supports the construction of future or imaginative events through retrieval and flexible recombination of past experiences into future scenarios. Tulving proposed that episodic memory permits mental traveling through subjective time (either as re-experiencing an old episode or "pre-experiencing" a future event) through the sense of self-knowing or "autonoetic awareness"/"autonoesis" (Renoult et al., 2019; Tulving, 1972, 2005). Conversely, semantic memory is associated with noetic awareness, or a state in which individuals have an awareness of the known, but there is no connection to their own experience with that thing (knowing) (Renoult & Rugg, 2020; Tulving, 2005). Finally, both systems share some key characteristics such as multimodal input, transmodal storage with representational information, flexible access and symbolically expressed stored information (Duff et al., 2020; Tulving, 2005).

## Box 1.3 Memory system

Memory	Sensory	Haptic Echoic Iconic
	Short-term	Working* memory Central executive Visuospatial sketchpad Phonological loop Episodic buffer
	Long-term	Declarative Episodic Semantic
Non-declarative Procedural Associative Non-associative Priming		

**Note:** This work focuses on declarative memory system (framed), although for discussion of language and memory interaction we must necessarily include working memory (marked with an asterisk). The table is adapted from Camina and Güell (2017), Repovš and Baddeley (2006), and Squire (2004)

### The semantic-episodic: distinction or unity?

One central (unresolved) question that is also of interest for language and memory relation is whether semantic and episodic memories are two systems or is there one declarative memory system (Baddeley, 2020; Duff et al., 2020; Fang et al., 2018; Renoult et al., 2019). In his original 1972 conception, Tulving suggested that these memory systems are not functionally distinct in a more profound sense. However, he later acknowledged these systems' functional distinction, proposing however that they are closely interdependent, continuously interacting, and partially overlapping (Renoult & Rugg, 2020; Tulving, 2005). Episodic memory requires the semantic memory system but also goes beyond it since the ability to “mentally travel in space” (supported by semantic memory) presents a precondition for mental time travel (supported by episodic memory) (Tulving, 2005). The constructive episodic simulation hypothesis (Schacter & Addis, 2007) also acknowledges semantic contributions to future thinking, while the "semantic scaffolding hypothesis" proposes that semantic knowledge acts like a framework facilitating retrieval of past episodes or thinking about future (Irish & Piguet, 2013). Even some authors propose that episodic memories represent a sequence of semantic representations, suggesting that episodes are retrieved through the semantic system (Fang et al., 2018). Recently, Irish and Vatansever (2020) proposed resolving

this semantic-episodic question by employing a gradient perspective. They argue that episodic and semantic memories can be perceived as lying on a concrete-to-abstract continuum within time, space and valence and a unitary neural memory system processes them. Empirical studies corroborate this interaction by showing that episodic memory processes can influence semantic memory retrieval (McKoon & Ratcliff, 1979; Renoult et al., 2015) vice versa (Mace et al., 2019; Sheldon et al., 2020; Tompary & Thompson-Schill, 2021).

The interaction between two systems and the constructive nature of the episodic memory system can be seen through the retrieval process. Namely, an episodic memory retrieval happens when a retrieval cue activates a representation sufficiently to elicit "pattern completion", bringing the representation to an active state (working memory). This constructive process (termed "synergistic ephory" by Tulving) uses elements both from the episodic (stored memory traces) and semantic memory (the cue) and results in the conscious experience of remembering. (Renoult & Rugg, 2020). Moreover, this semantic-episodic interaction could be supported by the overlap between their neural correlates (Burianova et al., 2010; Irish & Vatansever, 2020; Rajah & McIntosh, 2005; Renoult et al., 2019), as we will see in the following section. To sum up, the most recent studies argue against a hard semantic-episodic distinction (Irish & Vatansever, 2020). Therefore, throughout this work, when using the term "memory", we will be referring to the declarative memory system. When we want to characterize the type of representations and or awareness, we will use the terms "semantic" or "episodic" memory. Overall, we can perceive declarative memory as a cognitive system that supports binding the information from our experiences about the co-occurrence of people, locations, objects together with their spatial and temporal relations (Warren et al., 2018).

### 1.3.2 Memory network

Various descriptions of the neural representation of declarative memory system (regardless of its conceptualization) considered the hippocampus as the vital part of the network (Rugg & Vilberg, 2013). This structure plays a computational role supporting pattern separation/completion and operating with multidimensional information within spatial, temporal, and situational contexts. Additionally, it provides an interface between cortical networks coordinating and, hence the cognitive processes. It can adapt its functional relationships flexibly to the current behavioral goal (Reagh & Ranganath, 2018).

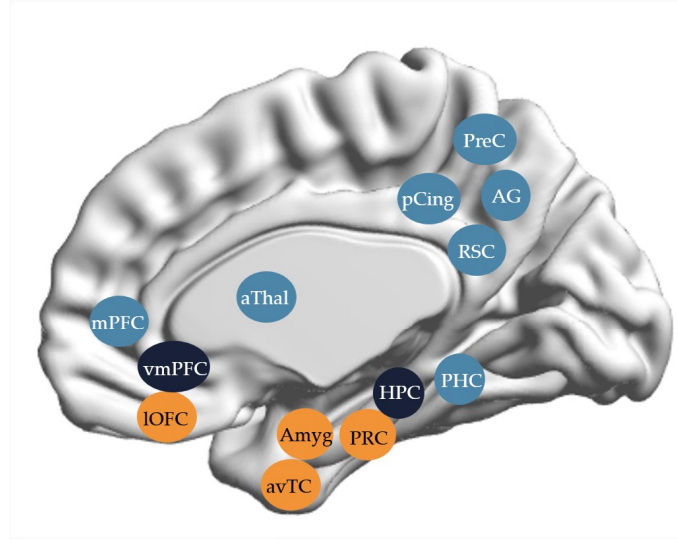
One of the neurocognitive models that proposes an interactive architecture of memory systems is the PMAT model (Ranganath & Ritchey, 2012; Ritchey et al., 2015). This model infers a posterior medial network (PM) and anterior-temporal network (AT). The PM comprises the parahippocampal cortex, retrosplenial, posterior cingulate, medial parietal, and ventrolateral parietal cortex. It encodes contextual associations that are a base for generating representations of the spatial, temporal, and broader causal relationships between elements of an event. On the other hand, the AT network comprises the perirhinal, ventral temporopolar, anterior fusiform, and lateral orbitofrontal cortices, as well as the amygdala. This network is involved in encoding semantic and perceptual information about the features and motivational significance of entities

(such as objects and people) (Ranganath & Ritchey, 2012; Reagh & Ranganath, 2018). The PMAT model also separates semantic domain into two qualitatively different and cortically divisible forms - perceptual and semantic knowledge supported by the AT network and relational semantic knowledge used for situation models supported by the PM regions (Reagh & Ranganath, 2018).

The PM and the AT networks are not mutually independent. They interact through bidirectional connections between the lateral and medial entorhinal cortex (Reagh & Ranganath, 2018). That way, the PM system supports contextual scaffold (at different levels – context, situation model, and schema), the AT system supports specific local representation along with emotional and semantic information, while the hippocampus integrates these elements as an event (Cooper & Ritchey, 2019; Reagh & Ranganath, 2018). Therefore, the hippocampus plays a unifying role by binding the features into a coherent representation and supporting flexible cortical retrieval. Nonetheless, the individual quality or feature is supported by cortical representation (Cooper & Ritchey, 2019).

Notably, the PM and AT have overlapping representations for similar situations and entities. Therefore, if the hippocampus fails to complete a pattern during episodic retrieval, semantic information will be generated. Conversely, if the hippocampus succeeds, the PM and AT will provide a pattern of activity similar to the one associated with the event (Reagh & Ranganath, 2018). Indeed, a reduced ability to retrieve episodic information is followed by more semantic details in the narratives of individuals with amnesic mild cognitive impairment relative to controls, probably as a compensatory mechanism (Seixas-Lima et al., 2020). The successful episodic retrieval is associated with the increase in connection of medial temporal regions (hippocampus) with left lateral frontal regions (IFG, dlPFC) and AG, posterior cingulate cortex, and precuneus (Cooper & Ritchey, 2019; King et al., 2015; Palacio & Cardenas, 2019).

During memory encoding, PMAT systems act in a modular fashion, with the hippocampus acting as a connector. However, during episodic retrieval, modularity decreases, and inter-network connections increase. In addition, both PM and AT dynamically increase their connectivity to the hippocampus as the episodic memory's multidimensionality increases (Cooper & Ritchey, 2019). Other researchers similarly suggested that various "process-specific alliances" (PSAs) support cognitive processes such as memory retrieval (Cabeza et al., 2018; Moscovitch et al., 2016). A PSA represents a set of regions that quickly group to mediate a cognitive process and afterward take part. Several PSAs support memory retrieval processes: semantic processing of the retrieval cue - a PSA grouping left vlPFC and left temporal cortex; memory search - a PSA between left dlPFC and dorsal parietal cortex; the reactivation of memory traces - a PSA of the hippocampus and posterior sensory cortices; the auto-noetic awareness - a PSA comprising all these regions and ventral parietal cortex (Davis et al., 2017; Moscovitch et al., 2016).



**Figure 1.5:** PMAT framework for memory and cognition proposed by (Ranganath & Ritchey, 2012). Blue regions are parts of PM system: mPFC = medial prefrontal cortex, aThal = anterior thalamus, pCing = posterior cingulate cortex, RSC = retrosplenial cortex, PHC = parahippocampal cortex. Red regions are part of AT system: IOFC = lateral orbitofrontal cortex, avTC = anterior ventral temporal cortex, PRC = perirhinal cortex, Amyg = amygdala. Regions in grey are possible sites of integration: HC = hippocampus, vmPFC = ventral medial prefrontal cortex. The figure is adapted from Ritchey et al. (2015). The regions are presented only schematically, and their position in the image does not fully correspond to their precise anatomical location.

Cognitive control is one of the crucial aspects of memory retrieval (Irish & Vatansever, 2020), and it was proposed that lateral PFC engages in the coordination of this process. Specifically, vlPFC is involved in updating and maintaining the content of working memory. Selection, manipulation, and monitoring of that information that is already active in WM engage dlPFC. These regions need to interact efficiently to achieve specific behavioral goals. Anterior PFC coordinates these processes (not the information). Moreover, anterior PFC switches between dorsal and ventral PFC processes to maximize performance and achieve behavioral objectives (Fletcher & Henson, 2001).

This anterior-posterior division of functioning within the memory system is also applicable to the functional specialization of the hippocampus along its long anterior-posterior axis. There was some evidence that the anterior hippocampus is related to encoding, while the posterior is related to retrieval (Spaniol et al., 2009). However, other findings suggest that the anterior hippocampus does not contribute uniquely to encoding and that encoding activity can be observed along the entire hippocampal long axis (for the discussion, see Poppenk et al., 2013). The current evidence suggests that the anterior part of the hippocampus supports more global, general information/gist-based conceptual information, while its posterior part supports fine-grained specific details/spatial memory (Irish & Vatansever, 2020; Poppenk et al., 2013; Reagh & Ranganath, 2018). Sheldon et al. (2016) also found differences in anterior-posterior hippocampal implication during semantic retrieval tasks. In their study, autobiographical categories recruited more anterior, while spatial categories engaged more posterior hippocampus. Nevertheless, the hippocampal functional specialization was recently

proposed to be better described through gradient than parcel or dichotomous representation (Przeździk et al., 2019).

Lately, this gradient perspective has also been applied to the general memory system (Irish & Vatansever, 2020). For instance, Bajada et al. (2017) proposed to comprehend functional specialization of the temporal lobe relying on its structural connectivity. These authors found two axis - medial to lateral and anteroventral to posterodorsal. The medial to lateral transition corresponded to the shift from episodic/emotion/spatial navigation functions to linguistic/semantic/auditory/visual processes. The anteroventral to posterodorsal axis was predominantly present in the lateral surface, and it mirrored the dorsal and ventral language pathways we previously described. These authors proposed that in the left hemisphere, anteroventral-posterodorsal axis reflected phonological-semantic processing, while in the right hemisphere, it reflected semantic-spatial processing. Irish and Vatansever (2020) proposed the default mode network (DMN) as the base for both memory systems based on the findings of Bajada et al. (2017) and the blurred boundaries between semantic and episodic retrieval (a more detailed description of large-scale networks will be in Chapter 4). The DMN was proposed as the joint basis for the two memory systems since it is situated at the end of unimodal to multimodal information cortical representation, supporting the integration of rich memory traces that can range from concrete to abstract features. That way, based on the behavioral goal, the events are reconstructed in various degrees of contextual richness and spatiotemporal specificity during retrieval (Irish & Vatansever, 2020; Seghier, 2013).

The subcortical level of the memory network is less defined than it is for language. Nevertheless, there are certain pathways that are principal candidates for this network, among them those forming hippocampal-diencephalic-cingulate networks (Bubb et al., 2017). For instance, studies consistently show memory engagement of fornix, directly connecting hippocampus and diencephalic structures (mammillary bodies, the anterior thalamus, and the hypothalamus) (Catani et al., 2013; Metzler-Baddeley et al., 2011). Its changes during aging are related to recollection and source retrieval performance (Herbet & Duffau, 2020). There is some evidence suggesting that the cingulum, the dorsal limbic pathway, connecting PM (specifically caudal cingulate gyrus with the hippocampus, prefrontal areas, and the rostral cingulate gyrus, Ranganath & Ritchey, 2012; Schmahmann et al., 2007) also plays a role in both recent and remote episodic memory (Irish et al., 2014; Wong et al., 2020). However, these results are inconsistent across studies and are found principally in patients, while they are not consistently replicated in neurologically healthy patients (Herbet & Duffau, 2020). Another limbic tract, the UF, connecting AT (Ranganath & Ritchey, 2012), specifically anterior and medial temporal lobes (temporal pole, entorhinal, perirhinal cortex, parahippocampal gyrus, and amygdala) and the inferior lateral and polar frontal lobes (orbitofrontal cortex and BA10) (Schmahmann et al., 2007), was previously associated with memory functioning (for a review on function and development of the UF, see Olson et al., 2015). However, it was found to be more implicated in associative learning than in episodic memory (Metoki et al., 2017). The role of UF in semantic retrieval is also not completely clear since some studies suggest that it has an unimportant role (Duffau et al., 2009), while others show its implication in retrieving proper names (Metoki et al., 2017). Therefore, the structural network underlying memory retrieval encompasses

numerous pathways, although their exact roles still need to be explored (Irish et al., 2014; Lockhart et al., 2012).

This overview provided us with the cognitive and neural map of memory and allowed us to precise our interest in it. We will now come back to our main question and present some evidence for language and memory interaction.

## 1.4 Examples of language and memory interaction

As we saw at the beginning of this chapter, cognitive processes were considered distinct psychological constructs with disparate neural bases. Therefore, their research paths were mainly parallel rather than crossed. Language and memory were not an exception (Covington & Duff, 2016). However, since language unfolds over time (Indefrey & Levelt, 2004), researchers became primarily interested in its relationship with working memory, especially during the execution of language processing (Baddeley, 2003; Duff & Brown-Schmidt, 2012; Kurczek et al., 2013). The relation between language and working memory has already been extensively researched and supported (Baddeley, 2003; Määttä et al., 2014; Vogelzang et al., 2017). At the same time, the relation between language and declarative memory was not equally under the spotlight. The traditional association of declarative memory to long-term storage instead of ongoing information processing, and the apparent manifestation of hippocampal damage in memory impairment, could explain this trend (Duff et al., 2020; Kurczek et al., 2013). However, evidence about language and declarative (episodic) memory started accumulating. For instance, Loftus and Palmer (1974) famously showed how formulation of questions and words could influence memory retrieval. Importantly, it showed the constructive nature of memory retrieval since language can affect combining elements into an episode during recall (Sternberg & Sternberg, 2012). Also, analyzing H.M.'s narratives on past events, MacKay et al. (1998) found that he showed less coherence and focus than controls. Researchers started exploring relationships between specific language processes and different memory types and proposing neurocognitive models of these relationships (Ullman, 2001). We will now present some evidence that supports and highlights some particularities of the interaction between language and memory both on the cognitive and neural levels. Box 1.4 summarizes raised questions regarding the language-memory relationship and the answers current literature provides.

### 1.4.1 Does memory only provide the content we express through language?

As we have seen, the development of language and memory through evolution was intertwined. It was suggested that language originated from the need to share one's inner world and knowledge (Corballis, 2019). But can the essence of their relationship be just that?

Research in developmental psychology provides an exciting insight. Namely, if language was only the expression of memories, then the pre-verbal memories should be easily translated into words with the development of language. Nevertheless, the evidence suggests that this is not such an easy transfer (Fivush & Nelson, 2004). For instance,

when two- and three-year-olds were asked 6 and 12 months after being engaged in a complex activity to recall it, they only used the words that were part of their productive vocabulary during the initial activity (Simcock & Hayne, 2002). These results suggest that the language skills during the original episode influenced encoding and subsequent verbal recall. The concept of context-dependent memories implies that some incidental elements of the event will also be encoded with the episode as a part of the memory trace. This context can also be a linguistic one, as in the case of bilinguals (Schroeder & Marian, 2014). Several studies showed that access to memories is better if subjects are using the same language during memory formation and retrieval (Larsen et al., 2002; Marian & Neisser, 2000), implying thus that language used in the time of encoding becomes a part of a memory, subsequently influencing retrieval. So even if language emerged from the need to express memories, it can also be a part of a memory trace.

### 1.4.2 Learning how to talk, learning how to remember, could they be connected?

If the phylogenetic development of language and memory was intertwined, is it also ontogenetic? The research on deferred imitation provides evidence on the way language develops by relying on declarative memory. In infants and toddlers, deferred imitation is considered a predecessor of declarative-like memory as it mirrors the child's ability to form internal representations (Heimann et al., 2006; Jones & Herbert, 2006). Previous studies found that deferred imitation was related to language development (Hayne & Simcock, 2008; Heimann et al., 2006; Kolling & Knopf, 2015). For instance, Sundqvist et al. (2016) found that deferred imitation at nine months predicted productive language at 16 months, while Heimann et al. (2006) showed that not only deferred imitation but also visual recognition memory and social communication skills relate to better communication skills at 14 months of age. To use words or gestures in communication, children need to learn them from somebody else (caregivers) and store their meaning in memory to use later in different situations (Heimann et al., 2006). Therefore, it was proposed that lexical development before the second year relies at least partially on the child's ability to form a mental representation of the experienced event and store it in long-term memory (Sundqvist et al., 2016).

On the other hand, there is also evidence that a child's language ability can influence memory performance. It was found that verbal cues provided by the adults facilitate memory retrieval in preverbal and early-verbal children, keeping in mind that in early language development, comprehension proceeds production (Hayne & Simcock, 2008). During the events that caregivers and children experience together, the adult helps focus the child's attention and organize the event into a coherent event using linguistic scaffolding. This linguistic support provided by the adult was associated with better recall by children. In addition, the extent to which parents talk about past events to their children and how elaborate their narration is related to the subsequent quality of their child's episodic narratives (Fivush & Nelson, 2004). Also, in preschool children, Klemfuss (2015) showed that language ability predicts delayed memory performance beyond age, initial encoding, and memory for a separate event, suggesting that language helps create a structure that children use later when reporting their memories. Finally, as we mentioned, episodic memory allows mental time travel, but how does



one develop the idea of time across which one can travel<sup>7</sup>? Since the concept of time is a social construction, children develop time concepts through communication or language (Fivush & Nelson, 2004; Hudson & Mayhew, 2008; McCormack & Hoerl, 2017). By engaging in conversations about past and future events in the context of recurring events, children are exposed to “temporal language”. Consequently, children map the conventional temporal terms on their long-term representations for sequences or recurring events (Hudson & Mayhew, 2008). Also, parents and caregivers orient children to take a temporal perspective for the events by talking with them about different time points (McCormack & Hoerl, 2017). This way, children’s memory for recurring events provides the base for developing temporal concepts that will be used to organize memories of past events, make predictions about future events, and make the difference between past, present, and future (Hudson & Mayhew, 2008). These findings show that language and memory develop through their interaction. In general, developmental research shows how language and memory functions lean on one another through ontogenesis.

### 1.4.3 How do we talk about our past?

As we have seen, language is used to communicate our inner world to others, our past episodes, or the future we imagine. While it is clear that declarative memory influences the content, or what we will say (i.e., can we remember the episodes, or can we imagine the future), can it also influence how we retell our story?

To produce a narrative, one needs to be coherent, organize information, coordinate a plan with respect to communication goals. In doing so, one cannot rely only on language but also engages memory capacities and executive functions (Seixas-Lima et al., 2020). We can thus assume that impairment of one of these processes should manifest in the individual’s narrative.

Indeed, patients with hippocampal damage and amnesia constructed narratives characterized by poorer temporal organization, cohesion and coherence (Kurczek & Duff, 2011; Race et al., 2015; Seixas-Lima et al., 2020). There is also evidence for a direct relationship between declarative (episodic) memory and word use. It was found that event narratives of patients with hippocampal amnesia across time (both past and future) had significantly fewer details, were less vivid (Hassabis et al., 2007; Race et al., 2011), and had fewer imageable words than healthy or brain-damaged groups (Hilverman et al., 2017). However, a recent study (Race et al., 2021) found that these patients can produce narratives using words as imaginative as those the controls used if there is a specific spatiotemporal context. Since the hippocampus is engaged in spatiotemporal coding, giving patients this type of cues might compel this structure, resulting in more vivid imagery (Race et al., 2021).

Regarding narratives that rely on semantic information, such as fairy tales, patients with medial temporal lesions use fewer details while guarding the main thematic line. In contrast, patients whose lesions also extended into the lateral temporal cortex showed

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<sup>7</sup>To have mental time travel, one also needs a concept of self and self-awareness. Unfortunately, we will not discuss the development of “self” here since it would surpass the objective of this work. For more on the subject of the development of memory, auto-noetic consciousness, and “self”, see Vandekerckhove (2009)

problems with both detail generation and story-line (Verfaellie et al., 2014). Similarly, the discourse of individuals with the amnesic mild cognitive deficit with episodic memory decline was associated with less coherence regarding episodic and semantic details, again suggesting the inter-dependency between episodic and semantic systems (Seixas-Lima et al., 2020). Overall, these studies show the linguistic influence of declarative memory can be observed both on discourse-level and single-words level.

#### 1.4.4 How do we communicate in everyday life?

The way an individual in a communicative context will formulate a message regarding a specific topic (e.g., Covid vaccination) will differ depending on who they are talking to (e.g., parent, friend, colleague). More precisely, it will depend on what the person thinks his interlocutor thinks, knows, or believes about the given topic. In other words, a prerequisite for meaningful conversation is maintaining the “common ground” with the interlocutor (Clark & Marshall, 1981). That way, common ground, consisting of each interlocutors’ knowledge about the other, provides a context within which an utterance is formulated (Brown-Schmidt & Duff, 2016). The concept of common ground is closely related to concepts of mentalization and theory of mind (Moreau et al., 2013; Premack & Woodruff, 1978).

Common ground, and hence language, is supported by multiple memory systems, one of which is declarative memory. It was initially considered that episodic memory is the most pertinent for forming a common ground during a conversation (Brown-Schmidt & Duff, 2016; Clark & Marshall, 1981). However, the idea that conscious representations could be acquired as fast as necessary to have a fluid conversation was challenged. Instead, a resonance-based theory proposes that working memory is also engaged in this process (Horton & Gerring, 2005). According to it, during a conversation, cues in working memory resonate in parallel with the information in long-term memory. If the overlap between cue and memory traces is sufficient, memories become accessible (Horton & Gerring, 2016; Horton & Gerring, 2005). The aforementioned is closely connected to the notion of episodic buffer (Baddeley, 2000) and synergistic ephory or even pattern completion (Renoult & Rugg, 2020). The resonance based theory distinguishes between two processes - commonality assessment referring to accessing information pertinent for common ground and message formation about that information. Both of these processes function by relying on declarative memory (Horton & Gerring, 2016). It was also proposed that this binding between multimodal input with representations from long-term memory is achieved by episodic buffer (Rudner & Rönnerberg, 2008). Brown-Schmidt and Duff (2016) explored referential communication in amnesic patients. Based on their findings, these authors concluded that some forms of the common ground could be supported by non-declarative mechanisms when evidence about it is present in the proximate environment. Nevertheless, they discovered that declarative memory is necessary for consistent referencing to shared information (Brown-Schmidt & Duff, 2016).

Additionally, research shows that common ground is integrated effortlessly in the early phases of speech planning, acting as a partial constraint (Vanlangendonck et al., 2016). It is constantly updated during communication since we learn some information only through conversation (Vanlangendonck et al., 2018). However, mentalizing network

(that supports common ground) is not active every time we communicate with somebody else. Instead, it only activates when there is a need to take common ground into account so that the formulated message is efficient (Vanlangendonck et al., 2018). Although not exhaustive, the presented review of studies (summarized in Box 1.4 testifies to a complex relationship between language and declarative memory across various domains. There are authors that tried to conceptually present this relation through models.

### Box 1.4 Summary of evidence of language and memory interaction

Section	Question	Conclusions	Supporting references
1.4.1	Is language just a means of expressing memory, or is it also part of memory?	<ul style="list-style-type: none"> <li>Language used at the time of encoding becomes a part of a memory, subsequently influencing the process of retrieval</li> </ul>	Fivush & Nelson, 2004 Larsen et al., 2002 Marian & Neisser, 2000 Schroeder & Marian, 2014 Simcock & Hayne, 2002
1.4.2	Are developmental paths of language and memory intersected or parallel?	<ul style="list-style-type: none"> <li>Lexical development is associated with declarative-like memory in children</li> <li>Linguistic scaffolding can help to organize an episode, encoding, and recall</li> <li>The concept of time, necessary for mental time travel, develops through communication and social interaction</li> </ul>	Fivush & Nelson, 2004 Hayne & Simcock, 2008 Heimann et al., 2006 Hudson & Mayhew, 2008 Klemfuss, 2015 Kolling & Knopf, 2015 McCormack & Hoerl, 2017 Sundqvist et al., 2016
1.4.3	Is the memory influence on talking about the past limited to details we can remember?	<ul style="list-style-type: none"> <li>Declarative memory functioning can have a linguistic influence both on discourse- and single-word levels</li> </ul>	Hassabis et al., 2007 Hilverman et al., 2017 Kurczek & Duff, 2011 Race et al., 2011; 2015
1.4.4	How memory helps us to formulate a message when we communicate with another person?	<ul style="list-style-type: none"> <li>A message within a communicative context is formulated based on shared common ground conversational patterns</li> <li>Episodic memory and its link to working memory have an essential role in formulating a message for conversational purposes</li> </ul>	Brown-Schmidt & Duff, 2016 Horton & Gerrig, 2016 Rudner & Rönnerberg, 2008 Vanlangendonck et al., 2018

## 1.5 Modeling language-memory interaction

We will present two contemporary models that appeared to us as the most pertinent for comprehending the language-memory relationship.

The first model that directly associates language and memory is the Declarative/procedural (DP) model proposed by Ullman (2001). Given that there is no definite evidence of the neural basis implicated exclusively in language and not in other cognitive functions, he postulates the co-optation hypothesis of language. According to this hypothesis, language should substantially depend on already extant neural systems regardless of whether they specialize for language during phylogenesis or ontogenesis (Ullman, 2016). Since language is learned, memory is the system that supports language learning, knowledge, and use. Specifically, Ullman proposes that declarative memory substantially supports an individual's linguistic knowledge, both at the level of words and more complex forms. In contrast, procedural memory is suggested to support sequences and rules in the language (grammar). Notably, he highlights that relying on this perspective and scientific knowledge about memory, we can make predictions about language functioning, which would not be possible using only language studies (Ullman, 2016).

The second model of interest is the MUC (Memory, Unification, Control) proposed by Hagoort (2005). Although not relying explicitly on the declarative memory system, this model provides a valuable framework for considering the language-memory relationship. Hagoort's model of language processing beyond single words is based on three components. The Memory component depicts knowledge about the lexical items (their phonological, morphological, and syntactic characteristics). The information within this component is coded differently from other information (e.g., visual), thus being language-specific. The Unification component accounts for the generative or combinatorial nature of language. These operations create larger structures from the elements retrieved from the first component. Hagoort distinguishes phonological, semantic, and syntactic unification that each engages a different part of left IFG. The Control component engages in attentional control and adapting the language to the current conversational context.

Even though these two influential models provide a basis for an understanding language-memory relationship, neither fully addresses language in a communicative context (Duff & Brown-Schmidt, 2017). While Ullman focuses on language by concentrating on lexicon and grammar (Ullman, 2016), Hagoort indeed invites to explore language processing "in its full glory" (p.1), suggesting to go beyond words (Hagoort, 2013). We agree with Hagoort's invite but believe that the full glory of language should also encompass its communicative function (for the discussion on the broadness of communicative phenomena, see Duff & Brown-Schmidt, 2017). Hagoort indeed talks about communicative context within the Control component of his model Hagoort (2016). However, he does not specify where the information for understanding this context comes from. Nevertheless, the Ullman's DP model provides essential "what" and "how" propositions regarding language and declarative memory interaction, while the Hagoort's MUC model supports the vital framework for modeling the dynamics of this interaction. We will discuss in more detail possible models of the language-memory relationship in the final chapter of this manuscript.

Considering that we are exploring this relationship from a cognitive neuroscientific perspective, the question that naturally follows is the neural basis of this relationship. Furthermore, can we talk about language and memory network?

## 1.6 Language and memory network?

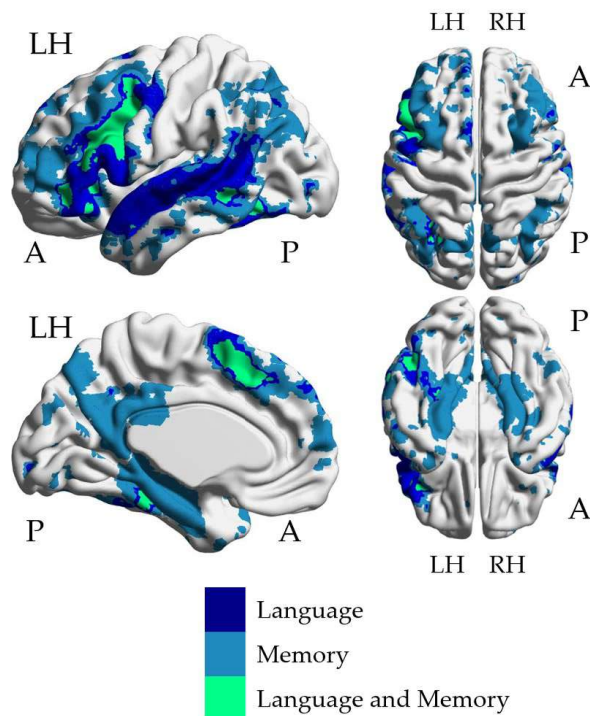
First of all, comparing the neural maps of language and declarative memory, we can distinguish certain regions where the two overlap. Figure 1.6 shows a possible common language and memory network (LMN) based on meta-analysis maps for terms "language" and "memory" obtained via the Neurosynth database (Yarkoni et al., 2011, <http://neurosynth.org>)<sup>8</sup>. We will only present this hypothetical network as the starting point for our work for the time being (see Figure 1.7 for the thematic map of chapters). The LMN is also supported on the structural level. As seen in the sections on language (1.2.2) and memory (1.3.2) networks, certain frontotemporal fiber tracks are engaged in both functions. Namely, the UF, connecting the anterior temporal and orbitofrontal area, has primarily been found to support episodic encoding and retrieval (Diehl et al., 2008) but has also been recognized as a part of the naming network (Duffau et al., 2014; McDonald, Ahmadi, et al., 2008). While the IFOF, known as a part of ventral semantic stream (Duffau et al., 2014), is also associated with amodal semantic processing, noetic, and subsequently auto-noetic consciousness (Moritz-Gasser et al., 2013), and verbal memory performances (McDonald, Ahmadi, et al., 2008).

Furthermore, there are other possible anatomical bases for this interaction. Namely, the central regions of episodic memory, the hippocampus, and the entorhinal cortex have connections with the structures that are engaged in the language. Specifically, a direct inter-hippocampal pathway projects the inferior temporal cortex (BA 37) connected with the inferior visual system to the hippocampus and transmits from the entorhinal to the temporal association cortex, temporal pole, and prefrontal cortex. Also, there is a polysynaptic pathway that projects the posterior parietal association cortex (BA 7) and the temporal cortices (BA 40, 39, 22) over the parahippocampal gyrus to the entorhinal area and conducts the hippocampal outputs via anterior thalamic nucleus to posterior and anterior cingulate and retrosplenial cortices (BA 29 and 30) (Duvernoy et al., 2013; Tracy & Boswell, 2008).

Although we will not discuss LMN in detail in this chapter, there is a structure that warrants more attention. Namely, we have already seen that patients with hippocampal damage do not experience only memory difficulties but also specific language impairments (see Section 1.4). Could it be that its function of binding elements into a representation exceeds memory domain and supports the interaction between language and memory?

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<sup>8</sup>Neurosynth is a platform that provides automatic meta-analyses of fMRI data. It uses fMRI studies and performs meta-analysis for a chosen psychological concept. It combines text mining, meta-analysis, and machine learning.



**Figure 1.6:** Language and memory network (LMN) resulting from the Neurosynth database. A search for terms language and memory in the Neurosynth database yielded 1101 and 2744 studies, respectively. Maps were binarized and added up. Dark blue = regions engaged in language, light blue = regions involved in memory, green = regions engaged in both functions.

### 1.6.1 Engagement of the hippocampus in language

Although the hippocampus was previously viewed as a critical structure within the episodic memory system (Rugg & Vilberg, 2013), studies suggest that the engagement of this structure is much more comprehensive than the episodic memory domain (e.g., Hilverman et al., 2017; Kurczek & Duff, 2011; Verfaellie et al., 2014). Indeed, studies report a hippocampal contribution to word retrieval during picture naming and word fluency tasks (Bonelli et al., 2011; Hamamé et al., 2014). Additionally, the same hippocampal theta oscillations that are vital for memory function were found for lexical-semantic aspects of sentence processing (Piai et al., 2016; Pu et al., 2020), while there are different results regarding their implication in syntactic integration (Meyer et al., 2005; Pu et al., 2020). Hippocampal theta oscillations reflect a mechanism for creating and retrieving "cognitive maps". Solomon et al. (2019) found that this hippocampal mechanism is also used for building the maps for semantic spaces based on representational distances between words. It is indeed proposed that the hippocampus engages in other cognitive domains the same way it supports episodic memory, through binding into flexible (re)constructions of relational representations or pattern completion (Cutler et al., 2019; Olsen et al., 2012; Rubin et al., 2017). Furthermore, it is suggested that the language-memory interaction might be associated with the role hippocampus plays in semantic memory and its capacity of predicting and simulating future events

based on past experience by the binding mechanism in the base (Duff et al., 2020; Pu et al., 2020). There is evidence that these hippocampal-dependent representations are rapidly available to influence ongoing processing - for instance, retrieving old episodes, creating new, and holding the representations online (Duff & Brown-Schmidt, 2017). Rudner et al. (2007) proposed that hippocampus engagement during episodic buffer processing reflects the binding of phonological representations in the working memory with semantic representations in the long-term memory. It is suggested that semantic impairments patients with hippocampal damage encounter reflect the inability to hold multiple diverse semantic features simultaneously as a cue to probe semantic memory effectively (Cutler et al., 2019). Nevertheless, Brown-Schmidt et al. (2021) recently found that bilateral hippocampal damage did not affect the ability to generate lexical-semantic mappings from spoken words (Brown-Schmidt et al., 2021). Instead of direct and necessary hippocampal implication in lexical-semantic mappings, these authors inferred that it contributes to semantic processing by maintaining the semantic network integrity throughout life. They also suggested that production is more demanding for the hippocampus than comprehension, in which it engages more when there is a need to link elements across time or sentences (Brown-Schmidt et al., 2021).

The literature review we have presented so far supports our claim that language and memory are closely connected. Specifically, it was shown that some parts of their cerebral networks overlap and share some structural pathways. A lot of this evidence came from research with patients with hippocampal damage and amnesia. Indeed, additional arguments on language and memory interaction come from studies on disorders where lesions occur in language regions, but symptoms appear in the memory domain or vice versa. This is a frequent scenario in several neurological, neuropsychological, and psychiatric disorders, such as post-stroke aphasia (Schuchard and Thompson, 2014) or conditions that cause auditory hallucinations (Ćurčić-Blake et al., 2017). However, temporal lobe epilepsy patients can also serve as a model for understanding language-memory interaction (Tracy & Boswell, 2008).

## 1.7 Temporal lobe epilepsy as a model for language and memory interaction

Epilepsy is a disorder characterized by recurrent seizures that manifest over a certain period (Schoenberg et al., 2011), alter cognition and behavior (Barr, 2015). This disorder is highly prevalent. For instance, Fiest et al. (2017) reported a point prevalence of 6.39 per 1000 persons and an annual cumulative incidence of 6.77 per 100000 people based on their meta-analysis. Of particular interest for this work is temporal lobe epilepsy (TLE). TLE represents 70-90% of epilepsy in adults, and it is characterized by seizures induced by the epileptogenic network (EN) centered on medial temporal structures, associated or not with hippocampal atrophy (Barr, 2015; Jaimes-Bautista et al., 2015; Thom & Bertram, 2012). Furthermore, these patients show deficits in both naming (Bartha-Doering & Trinka, 2014) and verbal and long-term memory (Bell et al., 2011; Tramonì-Negre et al., 2017) deficits. These difficulties are even more pronounced if the EN is located mesially (Alessio et al., 2006; Davies et al., 1998; Perrone-Bertolotti

et al., 2012; Zalonis et al., 2017). These characteristics of TLE make it a good model for exploring the language-memory relationship (see Box 1.5 for a summary). We will present the characteristics of TLE patients and the reorganization of their LMN in more detail in Chapters 3 and 4.

### Box 1.5 Arguments for considering TLE as a model for studying language and memory relationship

Available literature suggests at least four main reasons why patients with TLE should participate in studies exploring the relationship between language and memory functions and its neural basis:

1. Their epileptogenic network is centered on the temporal lobe that is essential in both language and memory;
2. TLE is often followed by hippocampal atrophy, and the hippocampus has a distinctive role in language-memory interaction;
3. TLE patients show cognitive deficits both in language and declarative memory domains, which allows exploring their relationship;
4. Due to high prevalence, TLE patients are more easily reachable than some other patient groups that could be of interest for this topic.

By combining psychological and neuroimaging evidence, cognitive neuroscience can provide a framework for unified cognition and brain functions models (Reagh & Ranganath, 2018). These models can then be used to pose both behavioral and neural predictions. Could our interactive and unified framework also have practical and clinical implications?

## 1.8 Benefits of the unified approach

Almost 30% of TLE patients have drug-resistant seizures and thus need surgery (Borger, Hamed, et al., 2021; Sherman et al., 2011). Standard surgical procedures (such as anterior temporal lobectomy) have shown to be generally efficient in terms of seizure freedom (Mohan et al., 2018; Téllez-Zenteno et al., 2005). Nevertheless, TLE patients sometimes “pay a considerable cognitive price” after surgery, which can have an impact on their life quality (Baxendale & Thompson, 2018; Helmstaedter, 2013). Meta-analysis performed by Sherman et al. (2011) showed that 44% of left TLE (LTLE) patients faced verbal memory and 34% naming decline. For that reason, a comprehensive neuropsychological and neuroimaging assessment is performed before surgery (for more details, see Chapters 3 and 5). The main goal of this evaluation is a cost-benefit analysis that reveals the risks of cognitive decline versus the potential seizure freedom (Massot-Tarrús et al., 2019).



Given the frequent memory and naming difficulties TLE patients face, standard pre-operative assessments inspect these functions as part of neuropsychological and neuroimaging assessment (Benjamin et al., 2017; Bonelli et al., 2010; Limotai et al., 2018; Trimmel et al., 2019). However, the interaction of these functions is neglected and they are considered separately. We have seen that cognition is not composed of isolated processes but rather a complex network of interactive functions (Kellermann et al., 2016; Tosi et al., 2020). We have also seen the complex relationship language and memory have both on the cognitive and neural level. Therefore, there is a presurgical assessment should focus on cognitive interaction. Additionally, as Kellermann et al. (2016) pointed out, the interaction between cognitive domains could be used when designing cognitive rehabilitation. For instance, bilingual older adults showed better memory performance than their monolingual peers (Schroeder & Marian, 2012). Understanding better how the language-memory interaction is achieved could lead to efficient rehabilitation plans. For instance, is it sufficient to work on executive functions to perform better in both language and memory domains (Kellermann et al., 2016; Schroeder & Marian, 2012), or could specific memory training contribute to language performance<sup>9</sup> and vice versa? Importantly, this could also inform prehabilitation planning to find and establish compensatory strategies before surgery to prepare for cognitive changes after it (Baxendale, 2020).

## 1.9 Thesis objectives

We established that interaction between language and memory spreads through the cognitive and neural domains, across phylogenesis and ontogenesis and that it is especially important for patients with TLE. Progress in comprehension of language processes and their neural bases was followed by progress in neurosurgical practice (Monroy-Sosa et al., 2021). In return, neurosurgery also contributed to further understanding of structural-functional relationships and the development of modern language models (Duffau et al., 2014). And we have seen at the beginning of this chapter that integration brings new findings that could not be found from isolated research. Therefore, exploring the interaction between language and memory could lead to progress both fundamentally and practically.

Thereupon this thesis has two goals:

- Mapping language-memory interactive network in the general population for reaching a more fundamental conclusion about neurocognitive functioning (Chapter 2 and 4)
- Investigating the reorganization and functioning of the language-memory network in TLE patients and whether it can have practical utility for presurgical examination (Chapters 3, 4 and 5).

Figure 1.7 provides a map of the present manuscript. To be precise, we are not proposing to reduce one function to another or a new function. Instead, much as contemporary

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<sup>9</sup>e.g., memory enhancement techniques proposed by Ullman and Lovelett (2018) that should improve learning of the second language based on Ullman's DP model.

cognitive neuroscientific perspectives, we are interested in the interaction between language and memory. How is it achieved at both cognitive and neural levels, how is it reorganized, and whether this perspective is beneficial in predicting postsurgical outcomes in patients with TLE?

Finally, several terms from the title of the thesis deserve further explanation. By *interactive mapping*, we wanted to highlight that tasks used in this work were designed so that the language-memory interaction is necessary. This is in line with previously presented and explained general principles of this work. *Multimodal assessment* refers to the fact that we will be relying on different types of neuroimaging, behavioral, and neuropsychological performance in this work. As neuroimaging data, we will be using anatomical, task-based, and resting-state fMRI, even though the REORG project within which this thesis was performed gathers other types of data (for instance, diffusion tensor imaging, DTI). Using multimodal data is not a new concept. Indeed, in the clinical setting, physicians (neurologists and neurosurgeons) consider data obtained by different neuroimaging methods (fMRI, PET, EEG) and neuropsychological assessment for every preoperative evaluation. Nevertheless, our objective was to highlight this aspect since leveraging the information obtained through different modalities may help detect some patterns or weak effects that might not be found using only one modality (Calhoun & Sui, 2016). In addition, the unimodal analysis might lead conclusions in the wrong direction, and using two or more modalities could help reach a valid conclusion. However, through our work, we will be using different approaches to data fusion, from analyzing data types separately and overlaying them (data integration), through using one set of data to constrain another (asymmetric data fusion) to using different modalities equally (symmetric fusion) (Calhoun & Sui, 2016). In the case of patients, it is of particular importance to correlate brain activity with behavioral and cognitive performances to evaluate reorganization efficiency. Moreover, multimodal data sets were found to be more helpful in predicting postsurgical outcomes in TLE patients than unimodal ones (Memarian et al., 2015).

The next chapter will first address how language and memory can be interactively mapped using an fMRI protocol.

1	<p><b>Ch 1. Theoretical introduction</b> Method: Literature review</p> <p>Main conclusions:</p> <p>Dynamic language-memory interaction is supported by a joint language and memory network - <u>LMN</u></p>	<p><b>Ch. 2 Mapping LMN in healthy individuals</b> Method: task-based fMRI + behavior data Analysis: GLM + parametric statistics</p>
2	<p>TLE patients have <u>reorganized LMN</u> since its key regions are affected by this disease which results in cognitive difficulties in these domains</p>	<p><b>Ch. 3 LMN reorganization in TLE patients</b> Method: task-based fMRI + behavior data + neuropsychological tests Analysis: GLM + nonparametric statistics</p>
3	<p>Exploring interaction of cognitive functions could have both <u>practical clinical</u> and <u>fundamental</u> implications</p>	<p><b>Ch. 4 LMN through the network prism</b> Method: task-based fMRI + resting-state fMRI + VBM + neuropsychological tests Analysis: Graph theory + nonparametric statistics</p>
		<p><b>Ch. 5 General discussion</b></p> <ul style="list-style-type: none"> <li>proposal of the language-memory interaction model and application for predicting postoperative cognitive outcome in TLE patients</li> </ul> <p>Method: task-based fMRI + resting-state fMRI + behavior data + neuropsychological tests + normalized volume Analysis: GLM + Graph theory + hierarchical clustering</p>

**Figure 1.7:** Thesis chapter overview. Colors indicate the conclusions reached upon in the introduction based on the literature review. Colors next to the chapter's title indicate which of them they will explore empirically.

## Chapter 2

# Mapping LMN in healthy individuals

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This chapter is based on the paper [Banjac, S., Roger, E., Cousin, E., Perrone-Bertolotti, M., Haldin, C., Pichat, C., Lamalle, L., Minotti, L., Kahane, P., & Baciú, M. \(2021\)](#). Interactive mapping of language and memory with the GE2REC protocol. *Brain Imaging and Behavior*, 15(3), 1562–1579.

## 2.1 Introduction

In the previous chapter, we argued and demonstrated evidence showing that the base of proper cognitive functioning is the dynamic interaction between different neuropsychological domains (Kellermann et al., 2016). Specifically, growing evidence suggests that memory and language influence each other more than previously thought (Duff & Brown-Schmidt, 2017; Moscovitch et al., 2016; Vogelzang et al., 2017). In general, we based our arguments for the language-memory interaction on several groups of findings showing:

- that language influences the formation of memories and remembering, while memory functioning can manifest through language production
- there are brain systems commonalities and communication paths between these functions
- lexical-semantic aspects of language are dependent on the declarative memory system, which is proposed to be accomplished through the hippocampus
- there are disorders, such as TLE, in which "memory regions" are impaired, but the symptoms also manifest in the language domain

This chapter presents the protocol developed within the REORG project (within which this thesis was performed)<sup>1</sup> for mapping the neural representations of the collaborative language-and-memory network (LMN). In the introductory part of this chapter, we will explain the general points that need to be considered for designing a protocol for mapping the interactive LMN. Even though in this chapter we will discuss the LMN mapping in the global population, in considering protocol design, we will also mention the constraints and necessities brought up by the clinical setting, since one of the goals of this work is to explore LMN reorganization in TLE patients and use these findings as part of the presurgical evaluation. Thus, the specific clinical demands significantly shaped the design of this protocol. Some aspects of the protocol that may be subject to criticism stem precisely from the fact that the protocol is designed to suit two populations - general and clinical.

### 2.1.1 Why fMRI?

The most widely used neuroimaging technique at the moment is functional magnetic resonance imaging (Silva et al., 2018). Addendum 2.1 provides an overview of the

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<sup>1</sup>The development of the GE2REC protocol within the REORG project surpasses the work performed in this thesis. It is the result of the team members' joint work.

fMRI basic principles, while Addendum 2.2 presents the main experimental designs and the underlying statistical analysis. We should highlight that these Addendums only introduce the main terms and concepts and are not exhaustive (i.e., they do not present the central physical principles underlying fMRI, nor all existing paradigms)<sup>2</sup>. To illustrate the broad representation and use of this technique, we performed a quick search of the PubMed database<sup>3</sup>. The results showed that among papers published between 2000 and 2021, the most common technique was fMRI (526139 studies), followed by Electroencephalography (EEG, 10989), Positron emission tomography (PET, 106715), Diffusion tensor imaging tractography (DTI, 12117) and Magnetoencephalography (MEG, 8623)<sup>4</sup>. Also, in the preoperative assessment of TLE patients, fMRI is regarded as an efficient tool (Szaflarski et al., 2017). There are several reasons for such a broad application of this technique.

First of all, there are no known dangerous side-effects linked with exposure to the magnetic field and radio waves employed by the MRI (S. Liu et al., 2015). Secondly, it is characterized by high spatial resolution, signal reliability, and robustness (Soares et al., 2016). Also, it allows mapping the whole brain and not just the areas exposed by craniotomy, which allows identifying a possible reorganization (Silva et al., 2018). However, this technique also faces several disadvantages such as substantial sensitivity to movement, lower temporal resolution due to the nature of BOLD signal (see Addendum Addendum 2.1). In addition, BOLD signal provides only an indirect measure of neural activity, compared to direct electrostimulation mapping (DEM Duffau, 2005). A patient's comorbidities can influence the quality and quantity of the data. Although most neurosurgical centers have a high field MRI at their disposal, there are practical restrictions on scanner availability and time limitations (Silva et al., 2018). Still, the presented disadvantages can be addressed using various statistical or technical aids. Three main goals of fMRI mapping of a function are identifying the network of engaged regions, lateralization (i.e., hemispheric predominance, see Chapter 3), and predicting the postsurgical change for patients (Benjamin et al., 2017). So the main question of this chapter is how should a paradigm be designed to map interactive LMN? However, to answer it, we must first see the guidelines and recommendations concerning paradigm design that stemmed from the separate study of language and memory.

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<sup>2</sup>These Addendums on fMRI are intended for readers unfamiliar with this technique so that they can follow subsequent text more easily. For a more detailed explanation, see Buxton (2013), Deichmann (2016), and Garavan and Murphy (2016).

<sup>3</sup>PubMed Central® (PMC) is an archive of biomedical and life sciences literature. It is maintained by The United States National Library of Medicine (NLM) at the National Institutes of Health. The search was performed on 11/09/2021.

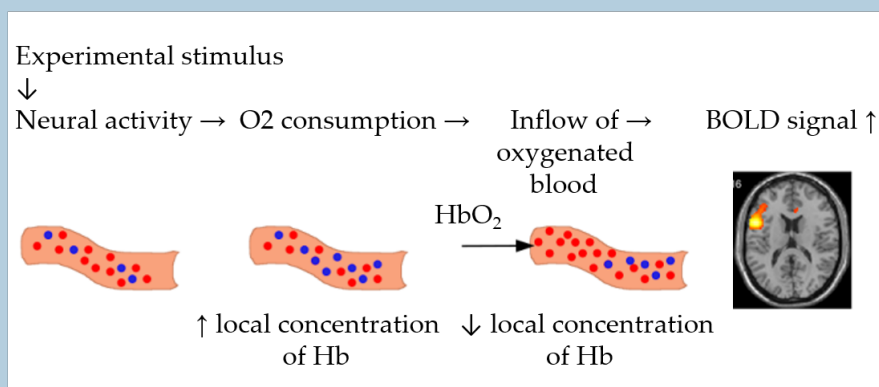
<sup>4</sup>The presented finding is by no means an exhaustive literature search but just an illustration. Proper systematic literature research should include several databases. Also, we did not perform a subsequent screening of the papers to distinguish between studies that used the technique, meta-analyses, methodological reports, etc.

### Addendum 2.1 Basic principles of fMRI

An increase in neuronal activity is associated with an increase in regional blood flow. fMRI (functional Magnetic Resonance Imaging) does not provide a direct measurement of this increase. Instead it is based on the concomitant functional changes in the magnetic properties of the blood that are happening at the level of the capillaries and the venous network, linked with the activated neurons. The fMRI is based on blood oxygen level-dependent or BOLD contrast that relies on two principles (Baciu, 2011; Buxton, 2013).

First, oxygen is carried by hemoglobin, the protein molecule in red blood cells. The magnetic properties of hemoglobin differ depending on oxygen concentration. While oxyhemoglobin (oxygen-carrying hemoglobin,  $HbO_2$ ) is diamagnetic, deoxyhemoglobin (hemoglobin without oxygen, Hb) is paramagnetic (Baciu, 2011; Deichmann, 2016).

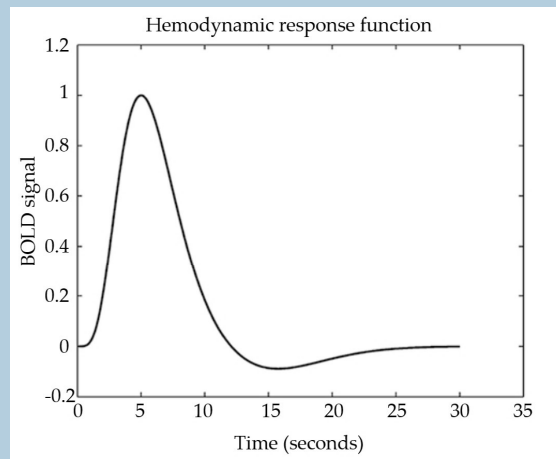
The second principle is “decoupling” that manifests during neuronal activation between the relative increase in blood flow and oxygen consumption. After the stimulus, active brain regions have higher metabolic demands and increased oxygen consumption, hence increasing deoxyhemoglobin concentration (see figure below). This is seen as an initial signal reduction or initial dip that lasts about 1-2s. After this, there is an increase in the flow of oxygenated blood to these regions than the less active ones (Amaro & Barker, 2006; Lindquist, 2008). Because more oxygen is supplied than consumed, there is a higher oxy-/deoxy-hemoglobin ratio, and the MR signal increases (Lindquist, 2008). Although a simultaneous increase in blood volume leads to a higher concentration of deoxyhemoglobin, there is still a relatively higher concentration of oxyhemoglobin. Increased oxygen distribution allows higher glucose metabolism, which gives more energy to a brain region used for task performance (Gazziniga et al., 2014). After this positive response, the metabolic rate of oxygen consumption and blood flow return to their baseline values. Since the relaxation of the blood volume is slower, there is an increased deoxyhemoglobin concentration seen as a post-stimulus signal undershoot.



Local changes in blood oxygenation occurring during brain activity. Figure adapted from Arias et al. (2017)

This behavior is called the hemodynamic response function (HRF). It is used to model BOLD signal: after initial dip (1-2s), the positive BOLD signal reaches its peak after 5-6 s, which is followed by a return to the baseline 10-12s after the stimulus, with a small undershoot before stabilizing again (25-30s after) (Deichmann, 2016; Lindquist, 2008; Soares et al., 2016).

MRI signal is sensitive to the difference in magnetic susceptibility between the intravascular and extravascular spaces induced by the presence of deoxyhemoglobin in the blood. The higher its concentration is, the greater the difference will be in magnetic susceptibility. When a population of neurons is activated, they will induce a local decrease in the deoxyhemoglobin concentration, thus a decrease in the magnetic susceptibility difference, which will increase MRI signal intensity (Baciu, 2011).



The hemodynamic response function. Figure adapted from Woolrich et al. (2016).

## 2.1.2 What do we know about language mapping?

There are between 10 and 19 primary language paradigms (depending on categorization Benjamin et al., 2018; Binder, 2016; Black et al., 2017). The choice of the language paradigm significantly influences the strength and reliability of activity lateralization and activation of regions of interest (Bradshaw, Thompson, et al., 2017). We will present here only the main points regarding the fMRI paradigms for language mapping. However, this presentation does not aim to be an exhaustive overview of this topic. Binder (2016) and Benjamin et al. (2020) provide more detailed representation regarding this subject.

Language paradigms predominantly employ a block design, and the most often used paradigm is verbal fluency (Benjamin et al., 2018), which was shown to be predictive of language impairment (Bonelli et al., 2012). However, dominant temporal resection does not impair this function, and it can even show postoperative improvement, while the most frequently observed cognitive deficit is naming decline (Sherman et al., 2011). This suggests that preoperative fMRI protocol for TLE patients should include a naming task. On the other hand, reviewing different language paradigms, the American Society of Functional Neuroradiology recommended using multiple tasks to map language function since one task cannot activate all dimensions language encompasses simultaneously (Black et al., 2017). Nevertheless, the tasks that were first in the proposed algorithms were Sentence Completion and Silent Word Generation. Indeed, numerous studies demonstrate the advantages of employing syntax-level tasks for a more robust characterization of language networks (Połczyńska et al., 2017), especially within the temporal lobe (Barnett et al., 2014). In addition, sentence generation tasks were found to elicit modest to high left-lateralization with good reproducibility on a



group level (Bradshaw, Thompson, et al., 2017).

As we declared in the introduction, we are interested in natural language. In the context of predicting patients' postsurgical cognitive outcomes, we are interested in patient's ability to communicate and not a specific linguistic function. Using the tests that access only lexical-semantic processes, the language complexity is not addressed (Duff & Brown-Schmidt, 2017; Hagoort, 2013; Połczyńska et al., 2017). On the other hand, we saw that the syntactic system rests upon and interfaces other linguistic systems (Matchin & Hickok, 2020). Therefore using syntax-level tasks should allow for a complete embrace of language processes (Barnett et al., 2014).

### 2.1.3 What do we know about memory mapping?

This short overview merely highlights the main points regarding memory mapping and is not exhaustive. See Agosta et al. (2016) and Buck and Sidhu (2020) for a more detailed discussion regarding this topic.

Due to its nature, in neuroimaging, long-term memory is usually broken down into its processes - encoding and retrieval (Pinango, 2006). That way, the cerebral network can be explored separately during memory formation and its recovery. Retrieval can occur either as a recollection or familiarity. The first refers to the recall of vivid and detailed episodes. Familiarity is a sensation that given information was already encountered without any contextual details about the episode (Buck & Sidhu, 2020). It was proposed that the hippocampus supports recollection, while the familiarity process is supported by the adjacent cortex (Diana et al., 2007; Eichenbaum et al., 2007).

Many memory fMRI paradigms rely either on the block or event-related design. The advantage of memory paradigms applying block design is that they detect the difference between task and the control condition more efficiently. However, using this design, one cannot use the information on response accuracy. On the other hand, although the event-related design is less powerful to detect a difference between different conditions, it allows exploring memory encoding or retrieval with respect to its success, and it prevents habituation and item expectations (Haag & Bonelli, 2013; Schmidbauer & Bonelli, 2020).

Material type (verbal vs. nonverbal) should be considered when designing the memory paradigm since it can affect activation lateralization. In general, verbal encoding tasks identify more left-lateralized activations, visual (such as color images or pattern encoding) more activation on the right side. In contrast, scene or face encoding elicits symmetrical activation. For presurgical evaluation of TLE patients, it is recommended to employ a paradigm eliciting bilateral activation of medial temporal structures in healthy individuals (Limotai & Mirsattari, 2012).

One of the most frequently used paradigms to study encoding or retrieval is the "Old/New" paradigm. Participants need to say if an item was previously experienced (old) or not (new) within this paradigm. However, we cannot know if the retrieval was based on familiarity or recollection in this type of task (Buck & Sidhu, 2020). For that reason, authors sometimes employ the "Remember/Know" paradigm for dissociating recollection and familiarity processes to find hippocampal activation (Diana et al., 2007). However, it was shown that the hippocampal response is not necessarily stronger for remembered than familiar items, and that it is associated with the amount

of contextual or episodic information encoded or retrieved rather than the strength of the memory signal (Rugg et al., 2012).

Another type is the recall-based memory paradigm that reflects more ecologically the scenarios of everyday memory. A participant is given a part of the episode as a cue for episode retrieval in these tasks. These paradigms often rely on covert responding (Buck & Sidhu, 2020).

Finally, in a paper providing guidelines for designing a memory fMRI paradigm, Buck and Sidhu (2020) recommend using both encoding and retrieval tasks to obtain a more robust mapping of memory networks. Since strong hippocampal activation is challenging to acquire on an individual level, including both of these processes can increase the sensitivity of a protocol.

Nevertheless, the requirements and recommendations specific for language and memory functions mapping are not the only ones that should be addressed when constructing an LMN protocol. Considering that one of our goals is to map LMN in TLE patients interactively, our protocol must also adhere to some specifics of the clinical setting.

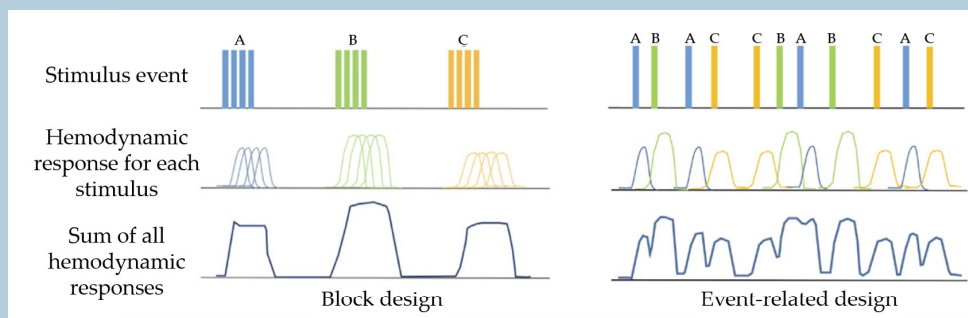
### Addendum 2.2 Analysis and design of fMRI experiments

There are two types of fMRI data - *task-evoked* and *resting-state*. Task-evoked fMRI explores brain activation for a specific cognitive function using a function-appropriate task. Resting-state fMRI explores the random activation pattern without an explicit task. The functional connectivity (i.e., co-activation of dispersed regions) can be explored using both task-evoked and resting-state fMRI data (see Chapter 4). Therefore, fMRI is essentially dynamic compared to lesion-based studies (Démonet et al., 2005). As it is impossible to assign brain activity to the intensity value of an image pixel, measurements obtained under different conditions need to be compared (Baciu, 2011). Hence, during task-based fMRI acquisition, participants perform several series of tasks alternately. The repetition of the measurements allows for improving the signal-to-noise ratio (Baciu, 2011).

The performed activities or tasks and the stimuli presented to a participant during a study are called *paradigms*. An fMRI paradigm usually consists of an active task eliciting a specific cognitive process (or processes) and a control task or rest that does not engage this process of interest. Although, studies showed that rest should be cautiously used since it is not free of neural activity (Binder, 2016; Garavan & Murphy, 2016). There are two main designs of task-evoked fMRI - block and event-related design (see picture below). For *block design*, the alternation of conditions (task/control or task/rest) is used to convolve the hemodynamic response. This design does not allow to isolate a cognitive event. Instead, it is averaged across a period.

In the *event-related* fMRI design, the hemodynamic response for every event is acquired separately. This design allows a researcher to select specific trials (e.g., excluding error events). In addition, it prevents habituation and guessing of the stimulus order, which cannot be prevented in the block-based design (Chen & Glover, 2015; Garavan & Murphy, 2016; Poldrack et al., 2011).

The task-based fMRI analysis aims to find the regions (or clusters of voxels) whose change in signal (fMRI time series) corresponds the best to the experimental manipulation. In this analysis, the stimulus timing function (i.e., experimental manipulation) is convolved with the HRF. Typically, the General Linear Model (GLM) is used to characterize the relationship between the experiment and the observed data using the standard formula:  $y(t) = \beta x(t) + \alpha + \varepsilon(t)$ . Where  $y(t)$  is the observed data (voxel time function),  $x(t)$  is the experimental manipulation,  $\beta$  is its scaling factor,  $\alpha$  is constant, and  $\varepsilon(t)$  is a random white-noise term. The parameters  $\beta$  and  $\alpha$  are fit by the linear regression method.  $\beta$  can be used as a measure of activation for each voxel. Additional regressors can also be added to eliminate undesired trends in the data, such as movements (Chen & Glover, 2015; Garavan & Murphy, 2016; Poldrack et al., 2011). The matrix containing all the factors is called the “design matrix”. Each column of this matrix corresponds to a specific experimental factor (e.g., condition) or control variables “of non-interest” (e.g., movements). Inferences about the effect of each factor are based on Student’s t or Fischer’s F statistics (Baciu, 2011).



Schematic representations of fMRI designs. Figure adapted from Arco et al. (2018).

#### 2.1.4 Clinical setting characteristics important for fMRI

The clinical setting we want our protocol to apply to is different from the standard experimental environment in many ways. First of all, by “clinical setting” in this manuscript, we refer to a hospital context where the primary purpose of neuroimaging or fMRI mapping is diagnostic evaluation and rehabilitation. Hence, the most crucial difference between that and the experimental setting is the participants. When designing a clinical protocol, one should have in mind the patients. An important aspect is a patient’s psychological and cognitive condition during the fMRI acquisition. The fMRI is based on the premise that participants perform the task. Thus the quality of the result directly depends on the participant’s performance (Buck & Sidhu, 2020; Petrovich Brennan, 2008). Neurosurgical patients usually have decreased neurocognitive functions (TLE patients are no exception, see Chapter 3), limiting their task comprehension and performance (Silva et al., 2018). Therefore the task must be achievable for patients because otherwise, the resulting activation map can be challenging to interpret (Petrovich Brennan, 2008). It is, of course, expected for patients to have poorer achievement than healthy participants, but the task should not be too

difficult for patients. That is especially important for event-related analysis, for which participants should have around 50% of correct responses for inter-subject performance variability and avoiding floor and ceiling effects (Buck et al., 2020). In addition, patient performance can also be affected by the anxiety, fear, and pain related to their pathology and neurosurgery possibility (Petrovich Brennan, 2008). If a task explores a specific function that patients know they have problems with, their anxiety might increase, affecting the MR signal (Benjamin et al., 2018). For this reason, implicit tasks are helpful for a memory paradigm as they reduce subjective pressure allowing for more favorable testing conditions (Caviezel et al., 2020).

Also, while the fMRI is familiar to an investigator, the procedures, sights, and sounds are unfamiliar for a patient. Fatigue increases, and attention drops with time spent in the scanner. Thus, when designing a protocol for clinical use, one should focus on isolating the process of interest, minimizing acquisition time, maximizing patient participation and cooperation while balancing the paradigm complexity (Buck & Sidhu, 2020; Silva et al., 2018). Therefore, to be appropriate for a clinical setting, a protocol should be short, easy to perform, and also easy to analyze (Cabrera et al., 2018).

Another crucial aspect of presurgical evaluation is the level of interest. In the clinical setting, an individual patient is the main interest, while studies on fMRI protocols usually report only group-level results (Aldenkamp et al., 2003; Buck et al., 2020; Deblaere et al., 2002), although some do illustrate individual-level activation (e.g., Benjamin et al., 2017; Binder et al., 2011). However, it was shown that group-level effects are not always relevant or valid on the individual subject level (Seghier & Price, 2016). Therefore, a presurgical protocol needs to demonstrate the ability to activate the main network and critical regions on an individual level. That is especially important for structures such as the hippocampus that is susceptible to geometric distortions, signal loss, and low signal-to-noise ratio (Buck & Sidhu, 2020; Haag & Bonelli, 2013; Powell & Duncan, 2005). Finally, the results of an fMRI protocol should be able to be integrated within a wider set of presurgical evaluations, above all neuropsychological scores, in order to interpret and comprehend a complex clinical image of a patient.

### 2.1.5 Is there an appropriate fMRI protocol for LMN mapping?

Following these short literature reviews, we believe that the answer to the posed question is negative for several reasons. First, the existing fMRI protocols are usually specially designed to elicit a specific process (e.g., phonological access or speech articulation, Binder, 2016). Second, although the standard preoperative assessment of TLE patients includes neuroimaging of language and memory functioning, the used protocols mainly focus on either language (Benjamin et al., 2017; Binder et al., 2011; Trimmel et al., 2019) or (episodic or verbal) memory processes (Bonelli et al., 2010; Dupont et al., 2010; Limotai et al., 2018). Despite promising results in predicting a postoperative decline, these studies do not address cognitive functioning holistically. Third, although the protocols that map both language and memory exist (Aldenkamp et al., 2003; Buck et al., 2020; Deblaere et al., 2002), they examine these functions separately, trying to segregate them rather than acknowledging their entanglement. Fourth, in the attempt to segregate a specific process, fMRI protocols can become very

distant from actual everyday behavior. However, for deciding on surgical treatment, it is essential to know if the obtained data is significant for everyday functioning in addition to its value for localization diagnostics (Helmstaedter et al., 1998).

The presented limitation of the existing protocols motivated the design of a new protocol within the REORG project. The main requirement for the new protocol is to include tasks that would elicit the language-memory interaction. In doing so, it should be acknowledged that language and declarative memory interaction is based on a widely distributed network (Roger, Pichat, et al., 2020). Hence, the protocol should map a network similar to the one we presented in the first chapter in Figure 1.6.

Moreover, this protocol would have to allow to map the structures that are of importance for these functions, but also those that are of significance for TLE patients – temporal lobe and hippocampus (Benjamin et al., 2017; Binder et al., 2011; Buck & Sidhu, 2020; Szaflarski et al., 2017). For this diagnostic purpose, an fMRI protocol should provide information regarding the dominant hemisphere, but also localization of language-and-memory network concerning potential epileptogenic zone (Ghosh et al., 2010). The summary of the introductory section is presented in Box 2.1. These points were used as a guide for protocol designing. The rest of the chapter will present and evaluate the GE2REC protocol originated from the REORG project. It consists of three tasks that are interconnected and based on language-memory interaction. GE2REC consists of a sentence generation with implicit encoding (GE) in the auditory modality and two recollection (2REC) memory tasks: a recognition (RECO) performed in the visual modality and a recall of sentences (RA). The objective of this study was to use this protocol to describe the LMN in healthy individuals.

### Box 2.1 Guidelines for interactive LMN fMRI protocol

- Using fMRI provides whole-brain mapping, suitable for wide networks including subcortical structures or identifying different reorganization patterns.
- Syntax-level language tasks allow for broader coverage of language processes and a more robust characterization of the language network.
- Using both encoding and retrieval memory tasks helps obtain a more robust memory network map and increases the protocol's sensitivity to hippocampal activation.
- A protocol applicable in a clinical setting must be short and easy to perform while mapping the crucial network and regions on an individual level.

## 2.2 Material and Methods

### 2.2.1 Participants

Twenty-one right-handed volunteers aged between 18 and 29 years ( $M = 21$ ,  $SD = 3.3$ ; 9 females) without neurological and psychiatric deficits were included in this study.

All participants were French native speakers and had a normal or corrected-to-normal vision. One participant was excluded from the fMRI analyses due to the high amount of artifacts in the data.

### 2.2.2 fMRI assessment of language and memory

The experimental protocol was developed using E-prime software (Psychology Software Tools, Pittsburgh, PA). Before entering into the magnet, the outline of the procedure was explained to participants. Importantly, they only received a complete description of the task in the GE run. For the 2REC runs, they were only informed about the general outline of the tasks and how they should respond, while they remained uninformed about the actual content of the tasks. A schematic illustration of all tasks is presented in Figure 2.1.

#### GE stimuli and task

During the GE run, the participants heard words through a headset. Their task was to covertly generate sentences after hearing a word related to the word they heard and continue producing the sentences associated with it until they heard the next word. The words were taken from the French standardized naming test D080 (Deloche & Hannequin, 1997). During the GE run, participants did not perform the picture naming task, but they produced the sentences in reference to the words they heard. The run included 5 task conditions of sentence generation performed in the auditory modality (8 stimuli/condition, 40 words in total) and the inter-stimulus intervals (ISI) that lasted 5 s intended to provide enough time to generate a correct sentence. The run also included five control periods (non-generation) to control for auditory activations during which a pseudoword was played eight consecutive times, with 5 s ISI. The participants were asked to listen to the pseudoword and not to talk covertly. The run also included five rest blocks with a fixation cross displayed for 10 s, placed directly after the generation blocks to allow the hemodynamic response to come down. Participants were required to fixate the cross. The order of conditions was Task (Generation), Rest, and Control. The total duration of the run was 7.3 min.

#### RECO stimuli and task

During the RECO run performed in the visual modality, the participants were shown pictures on the screen, and their task was to respond whether they heard the names of the objects in the images during the GE run. The event-related design was used, including pictures of the words participants heard in the previous task, pictures of the new objects, control images, and rest conditions. All presented images were real-life equals of the pictures from the DO80 (Deloche & Hannequin, 1997). The run included 40 pictures of the words presented in the GE run (henceforth OLD). The participants were instructed to press the “yes” button on their response box in their dominant hand when they saw the image corresponding to one of the words they heard in the previous run. Additionally, the run included 40 pictures of the words not presented in the GE run (henceforth NEW). These NEW items (pictures) presented the words that were also taken from the DO80, and these words were matched with the words

presented in OLD pictures in terms of lexical length and frequency. The participants were required to press the “no” button on their response box when they saw the image showing the object whose name they did not hear in the previous run. The run also included 40 control images showing the button that needed to be pressed to control the motor activations during button pressing. Furthermore, the run contained 45 null events represented by a fixation cross. The ISI during the RECO task was 2.5 sec, so all events were displayed during 2.5 sec, and conditions were presented in pseudo-randomized order. The total duration of the run was 6.8 min. We employed the event-related rather than block design since the former has been shown to identify the effects of successful encoding well (Haag & Bonelli, 2013) and to avoid the prediction of stimuli. Importantly, there is a modality change between GE (audio) and RECO tasks (visual) to enhance the access to episodic memory and, accordingly, the activation of hippocampal structures.

### RA stimuli and task

During the RA run, the participants heard the words they heard previously in the GE run through a headset. Their task was to recall and covertly repeat the sentences they had generated for each word in the GE run and to continue repeating them until hearing the next word. A block design was used, including task and rest conditions. The run included 5 task conditions of recall performed in the auditory modality (8 stimuli/condition, 40 words in total) with 5 s ISI. The run also included five rest blocks in the visual modality represented by a fixation cross displayed for 10 s, and participants had to fixate the cross. The total duration of the run was 4.17 min. Since fMRI is highly sensitive to motion (Powell & Duncan, 2005), we have chosen to use covert production in GE and RA runs. This is a commonly used version of the production task (Black et al., 2017) that has been proven to provide reliable activation of language regions and lateralization (Benjamin et al., 2017; Haag & Bonelli, 2013).

### 2.2.3 MR Acquisition

Functional MRI was performed at 3T (Achieva 3.0T TX Philips Medical systems, NL) at the IRMaGe MRI facility (Grenoble, France). The manufacturer-provided gradient-echo/T2\* weighted EPI method was used for the functional scans. Forty-two adjacent axial slices parallel to the bicommissural plane were acquired in sequential mode (3mm thickness, TR = 2.5 s, TE = 30ms, flip angle = 82°, in-plane voxel size = 3 × 3 mm; field of view = 240 × 240 × 126 mm; data matrix = 80 × 80 pixels; reconstruction matrix = 80 × 80 pixels). Additionally, for each participant, a T1-weighted high-resolution three-dimensional anatomical volume was acquired by using a 3D T1TFE (field of view = 256 × 256 × 160 mm; resolution: 1 × 1 × 1 mm; acquisition matrix: 256 × 256 pixels; reconstruction matrix: 256 × 256 pixels).

## 2.2.4 Data processing

### Behavioral analyses

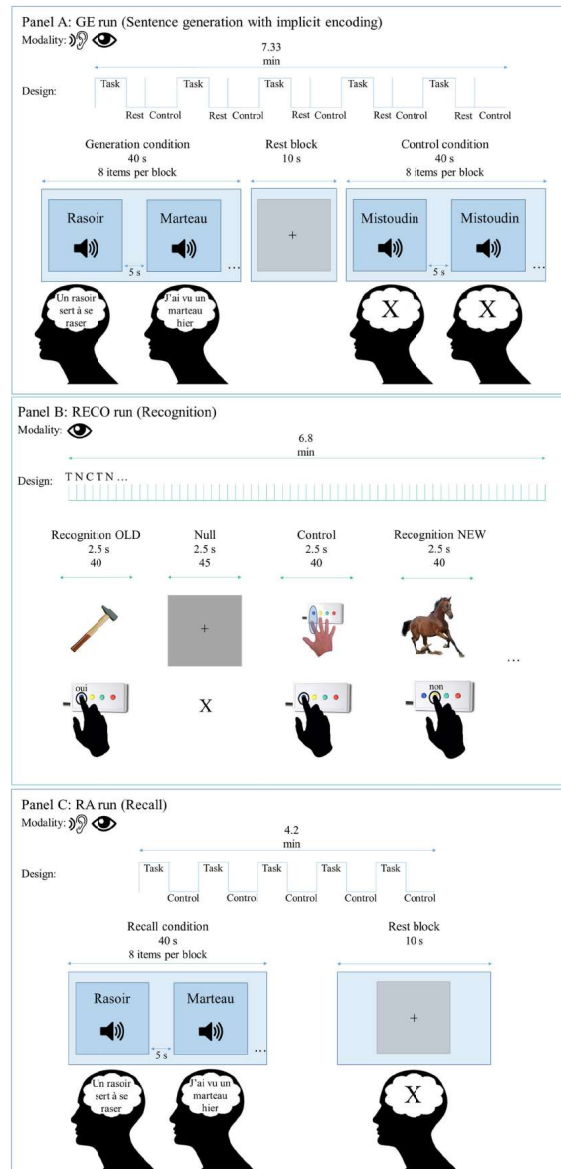
We calculated behavioral performances during the recognition task (%CR RECO) based on the responses during the RECO run. The encoding performance during GE was indirectly determined via recognition (RECO). Based on of the %CR RECO for old items, we identified those that were successfully encoded among all items presented during GE. Statistical analyses were performed using RStudio software version 1.1.456 (RStudio Team, 2016). All one-sample and paired t-tests were computed with the "t.test" function in the "stats" R package version 3.5.1 (R Core Team, 2018).

### Functional MRI analyses

The Analyses were performed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK) running under Matlab R2015b (Mathworks Inc., Sherborn, MA, USA).

**Preprocessing steps** . Functional MRI volumes were first time-corrected with the mean image as the reference slice to correct artifacts caused by the delay of time acquisition between slices. After that, all time-corrected volumes were realigned to correct the head motion. The T1-weighted anatomical volume was co-registered to mean images obtained through the realignment procedure and normalized to MNI (Montreal Neurological Institute) space. The anatomical normalization parameters were subsequently used for the normalization of functional volumes. Each functional volume was smoothed by an 8 mm FWHM (Full Width at Half Maximum) Gaussian kernel. Noise and signal drift was removed by using a high-pass filter (1/128 Hz cutoff). Preprocessed data were then statistically analyzed.





**Figure 2.1:** Schematic illustration of the GE2REC protocol. Panel A: GE (Sentence generation with implicit encoding) run with block-design. Items were presented in auditory modality during Task (word to generate sentences) and Control (pseudo-word) and in visual modality during Rest (central cross to fixate). Participants were required to generate sentences during Task covertly and to do nothing during Control. They fixated the cross during Rest. Examples of French items are shown (rasoir=razor; marteau=hammer; mistoudin is a pseudo-word). Panel B: RECO (recognition) run with the event-related design. Items were presented in visual modality during Task (images to recognize), Control (images to be repeated), and Null events (central cross to fixate). Participants were required to recognize whether or not they had heard the object presented in the image and reply by using the response box. They were asked to press the button shown in the picture and fixate the cross during the Null event during the Control. Panel C: RA (Recall) run with block-design. Items were presented in the auditory modality during Task (word to recall sentences) and in the visual modality during Rest (central cross to fixate). Participants were required to recall the sentences they generated in the GE run and to covertly repeat them. They fixated the cross during Rest

**Functional MRI statistical analyses** . We evaluated GE and RA runs by analyzing them as a block design. In contrast, encoding during sentence generation (ENCO) was analyzed using the GE run but as an event-related design by comparing those GE items that were correctly recognized during the RECO run to those that were not correctly recognized. In the same vein, the recognition was evaluated by analyzing the RECO run as event-related, comparing the correctly recognized items with the ones that were not correctly recognized, as well as comparing correct recognition of OLD and NEW items. Statistical parametric maps were generated from linear contrasts between the HRF parameter estimates for the different experimental conditions. The whole-brain effects of interest were firstly evaluated at an individual level (first-level): (1) effect of language by comparing sentence generation and control; (2) effect of memory encoding during sentence generation by comparing the correctly and incorrectly encoded items; (3) effects of memory recognition by comparing correctly with incorrectly recognized items; (4) differences in recognition by comparing recognition of old and new items and (5) effects of memory recall by comparing sentence repetition with the baseline. Six movement parameters obtained by realignment corrections were included as noise (regressors of non-interest).

For the second-level group analysis, individual contrasts were entered into a one-sample t-test and activations were reported at a  $p < .05$  significance level with the FWE correction ( $T_{GE} > 6.5$ ;  $T_{ENCO} > 6.52$ ;  $T_{RECO} > 7.03$ ;  $T_{RA} > 6.54$ ) for all effects. These second-level group analyses were also repeated with a more permissive threshold ( $p < .001$  uncorrected) to test if the activation can be identified in regions expected to be engaged in language and memory processing by previous studies and models. An additional reason for threshold lowering is that one of the hub regions of the LMN, the hippocampus, and mesial temporal structures in general, can be affected by geometric distortions and signal loss (Buck & Sidhu, 2020; Haag & Bonelli, 2013; Powell & Duncan, 2005).

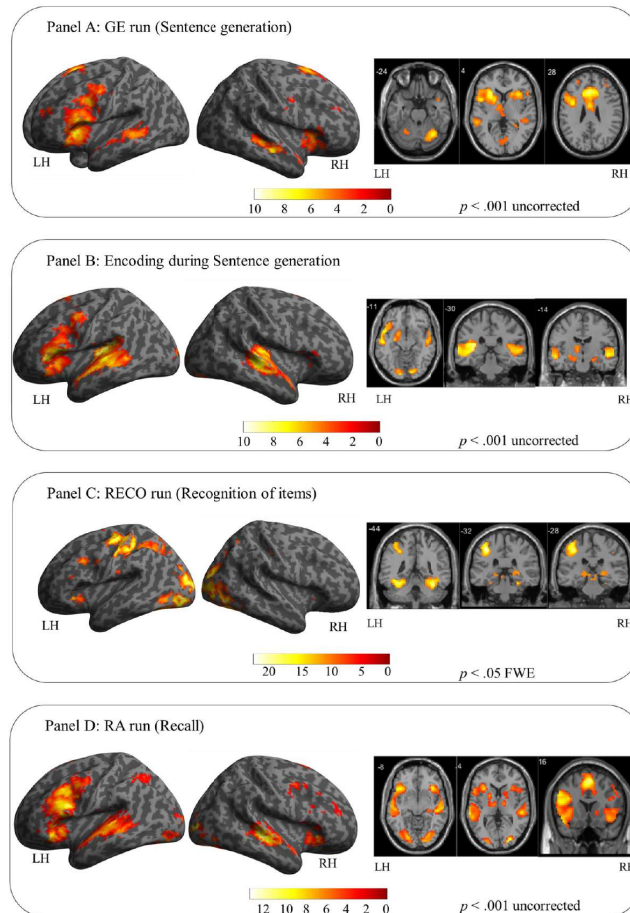
## 2.3 Results

### 2.3.1 Behavioral results

During the RECO run participants correctly recognized on average 72.62% (SD = 10.2) of old items and correctly rejected on average 87.87% (SD = 7.36) of new items. The correct recognition of old items and the correct rejection of new items were both above the chance level ( $t(20)_{OLD} = 10.16$ ,  $p < .001$ ;  $t(19)_{NEW} = 23.02$ ,  $p < .001$ ). Paired t-test demonstrated that the recognition of old items ( $M_{RT\_OLD} = 0.97$ ; SD = 0.07) was faster ( $t(19) = -5.51$ ,  $p < .001$ ) than the rejection of the new ones ( $M_{RT\_NEW} = 1.1$ ; SD = 0.07).

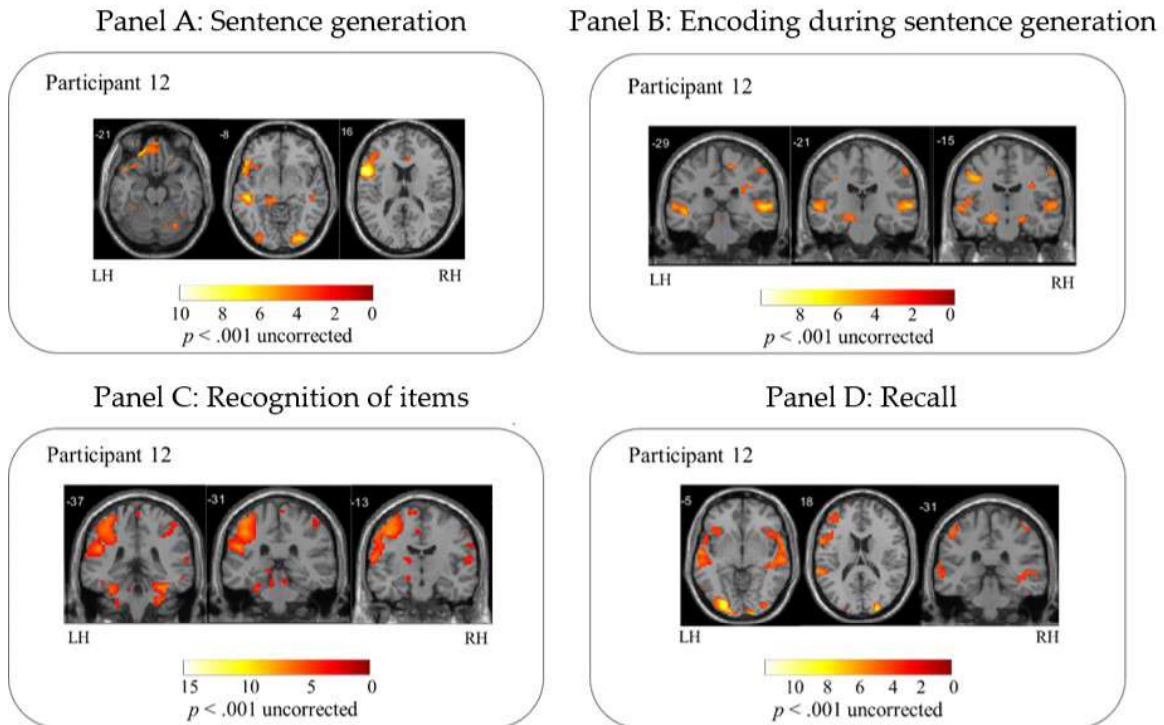
### 2.3.2 Functional MRI

Since the present chapter aims to validate the GE2REC protocol in healthy individuals, we will present the second-level group results (see Figure 2.1 and Appendix A for the lists of activated regions). However, as mentioned, a protocol applicable in a clinical setting should also map the same network on an individual level. Therefore Figure 2.3



**Figure 2.2:** Illustrative overview representation of global activation obtained for sentence generation (panel A), encoding (panel B), recognition of items (panel C), and the recall (panel D). Activations for each task were obtained at a group level ( $N = 20$  participants for all tasks except recognition of items where  $N=19$  were included due to a lack of responses of one participant). Activations were projected onto the lateral left and right views of surface rendering and 2D coronal and axial slices. The left (LH) and right (RH) hemispheres are indicated. The color scale indicates the T value of the activation. The GE, RA, and ENCO results were depicted in a more permissive threshold ( $p < .001$  uncorrected) to illustrate activations that were obtained on this significance level. The presented coronal slices for the encoding during sentence generation were chosen so that they show anterior ( $y = -14$  mm) and posterior ( $y = -30$  mm) hippocampus (Poppenk et al., 2013).

illustrates such an analysis in one participant. The list of activations is presented in Table A.1.



**Figure 2.3:** Illustration of the GE2REC individual-level results. The figure represents an example of activations obtained in one participant for sentence generation (panel A), encoding during sentence generation (panel B), recognition of items (panel C), and recall (panel D).

### Sentence Generation (GE)

The GE task vs. control comparison is presented in Panel A of Figure 2.2 and Table A.2. Overall, the results reveal bilateral but predominantly left activation of a vast fronto-temporo-parietal network, including left prefrontal, inferior frontal, bilateral insula, and right precuneus. The activation of left superior temporal and bilateral middle temporal and superior temporal pole cortices was also observed together with right cerebellum Crus 1 and VI.

### Encoding during the sentence generation (ENCO)

The correct encoding of the items during the generation of sentences activated expected language regions such as the left inferior frontal and bilateral middle and superior temporal cortices. Bilateral hippocampal activation was also detected with a lower significance level ( $p < .001$ ). These activations are presented in Panel B of Figure 2.2 and Table A.3.

### Recognition (RECO)

During the recognition task (task vs. control), the correct retrieval process activated an extensive frontal-temporo-parietal network shown in Panel C of Figure 2.2 and Table A.4. The identified network included bilateral fusiform gyri and occipital cortices, left inferior and superior parietal cortices, left cingulum, medial prefrontal cortex, left inferior and orbitofrontal gyrus, left insula and bilateral hippocampi. Bilateral parahippocampal activation was also detected with a lower significance level ( $p < .001$ ). Correct recognition also activated bilateral cerebellum IV-V and VI as well as left lobe Crus 1.

### Differences in recognition

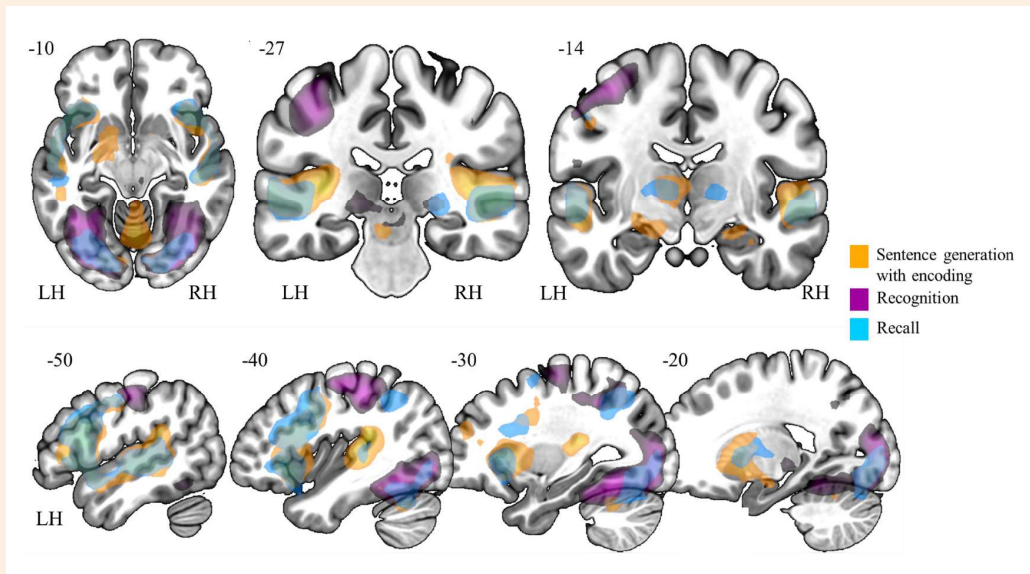
Comparing two types of items showed that the recognition of old items engaged more the left parietal cortex, notably precuneus, cuneus, AG, and bilateral middle cingulate and middle temporal cortices. Conversely, correctly rejecting new items compared to correctly recognizing old ones activated more bilateral fusiform and occipital regions. The activations are presented in Table A.5.

### Recall (RA)

The recall process (recall vs. baseline) activated a network presented in Figure 2.2, Panel D, and Table A.6 consisting of left inferior frontal and bilateral predominantly right-oriented prefrontal and medial frontal cortices and left insula. Bilateral activations in the temporal superior and middle cortices and the left temporal pole were also identified. The activation of the parietal regions consisted of the left inferior parietal and angular gyrus, while the activations of the cerebellum were limited to right Crus 1. Right hippocampal activation was also detected with a lower significance level ( $p < .001$ ). Although the RA task was designed to explore the interaction of language and memory, to check if this task indeed engaged memory in addition to language processes, a paired t-test was conducted testing for activation differences between RA and GE tasks. This analysis indicated that the RA task engaged more bilateral lateral and medial parietal regions and the right hippocampus when employing a lower significance level ( $p < .001$ ), as shown in Table A.7.

**Box 2.2 Summary of the main results**

- Sentence generation with implicit encoding activated bilateral temporal, left frontal regions, and bilateral hippocampi;
- Correct recognition of the items activated inferior bilateral occipitotemporal left parietal, bilateral hippocampal, and parahippocampal regions, as well as the left frontal inferior and SMA;
- Recall activated extensive fronto-temporo-parietal network with the right hippocampus.



Illustrative overview of the synthesis of results obtained with GE2REC protocol during sentence generation with encoding (orange), recognition of items (violet), and recall (blue). The activated regions are projected onto 2D anatomical slices presented in axial, coronal, and sagittal orientations. The left (LH) and right (RH) hemispheres are indicated.

## 2.4 Discussion

To explore language-memory interaction, we need an adequate tool that would be able to capture this synergy in action while being adapted to both clinical settings and empirical research standards. To this end, the GE2REC protocol was developed within the REORG project for interactive mapping of the language-and-memory network. In this chapter, we present its validation in healthy individuals.

### 2.4.1 Sentence generation and encoding

Our results indicate that sentence generation activated an extensive bilateral but predominantly left fronto-temporo-parietal network. Despite the covert production, this

network included left inferior frontal (pars opercularis and pars triangularis), left insula, and bilateral SMA usually required by the production of sentences (Grande et al., 2012; Haller et al., 2005; Menenti et al., 2012; Price, 2012; Segaert et al., 2012). The inhibition of articulation could explain the activation of the anterior cingulum (Løevenbruck et al., 2018; Price, 2012). Additionally, superior and middle temporal gyri as well as the superior temporal pole were activated, which is in line with other results reporting syntactic, lexical-semantic, and phonological demands during a sentence generation (Grande et al., 2012; Indefrey & Levelt, 2004; Menenti et al., 2012; Price, 2000; Segaert et al., 2012). Nevertheless, apart from the right precuneus, the GE task did not elicit activations in standard language parietal regions (Binder & Desai, 2011; Price, 2012). The reason could be that this task did not put too much demand on phonological processing (like rhyming tasks do) and speech comprehension (Cousin et al., 2007), nor did we use a standard semantic contrast (Binder et al., 2009).

The successful encoding during sentence generation showed the bilateral hippocampal activation on a more permissive threshold ( $p < .001$ ), which is in line with previously reported findings (Diana et al., 2007; Preston & Eichenbaum, 2013; Spaniol et al., 2009). Also, the obtained hippocampal activation tended to be rostral (anterior), in line with previous studies and models (Lepage et al., 1998; Preston & Eichenbaum, 2013; Spaniol et al., 2009). Employment of the permissive threshold can be justified considering that fMRI acquisition of the medial temporal lobe can be affected by geometric distortions and signal loss (Buck & Sidhu, 2020; Haag & Bonelli, 2013; Powell & Duncan, 2005). We see a higher anterior superior temporal activation when comparing successfully with unsuccessfully encoded items than when comparing all sentence production with the control. This area corresponds well with the auditory word form area and is a part of the lexico-semantic network (Hertrich et al., 2020; Price, 2012). This difference between the tasks could suggest that the words that were better encoded were in fact better the words participants did not have a problem hearing, recognizing, and find in their mental lexicon.

## 2.4.2 Recognition and naming

The modality change between GE (auditory) and RECO (visual) run was implemented in this protocol to elicit participants responses based on recognition rather than familiarity, activating thus episodic memory (Perrone-Bertolotti et al., 2015). As mentioned, with the “Old/New” type of tasks, there is a possibility that participants perform this task based on familiarity instead of recollection (Buck & Sidhu, 2020; Diana et al., 2007). However, we believe that our participants indeed relied on recollection and that their retrieval had the form of vivid and detailed episodes. The reason is that the identified network, including parahippocampal gyri, thalamus, parietal, and prefrontal cortices, resembles the PM network proposed by Ranganath and Ritchey (2012) that engages in recollection. Additionally, the identified posterior bilateral hippocampal activation is in line with studies suggesting its role in integrating the elements in a coherent episode (Cooper & Ritchey, 2019; Reagh & Ranganath, 2018) and those connecting more posterior hippocampal activation to retrieval (Spaniol et al., 2009). The obtained bilateral prefrontal activation also agrees with previous findings (Spaniol et al., 2009). Additionally, we found expected differences between correctly identified

old items and rightly rejected new items reflected in reaction time and left parietal activation (Guerin & Miller, 2009).

Although participants were instructed only to respond if they remembered the presented item, we believe they also automatically named a picture upon seeing it based on the obtained activation. While previous studies connected the activation of the fusiform gyrus, inferior frontal cortex, and insula with memory processes (Aldenkamp et al., 2003; Spaniol et al., 2009), we believe that in this task they may reflect a verbal strategy used by participants to perform the task which included picture naming. Activations found in the IFG, SMA, insula, fusiform and parietal cortices correspond well with the picture naming network (Duffau, 2014) and are a part of AT memory system engaged in semantic declarative memory (Ranganath & Ritchey, 2012; Reagh & Ranganath, 2018). Additionally, identified cerebellar activations, specifically Crus 1 and lobules IV-V and VI, correspond to language processes (Keren-Happuch et al., 2014; Price, 2012; Stoodley & Schmahmann, 2018). This finding concurs with the studies arguing that our behaviors engage intertwined processes and that experimental tasks may recruit functions incidental to task demands (Poldrack & Yarkoni, 2016; Price & Friston, 2005). The endeavor of trying to separate functions can be artificial. Instead, efforts should be directed towards the comprehension of the interaction of the cognitive functions.

### 2.4.3 Recall and sentence generation

Finally, the RA task was designed to directly assess the interactive dynamics of language-and-memory while also being close to everyday experiences by having a more natural recollection scenario (Buck & Sidhu, 2020). The RA activations of the left inferior frontal gyrus, bilateral SMA and insula, as well as bilateral superior and middle temporal cortices and Crus 1 of the cerebellum resembled the ones found during generation and can be related to the language component of the network (Hertrich et al., 2020; Hickok & Poeppel, 2007; Price, 2012). On the other hand, the activations of the bilateral prefrontal and predominantly left parietal cortices, as well as bilateral fusiform gyri, are in agreement with the previous results on memory retrieval (Aldenkamp et al., 2003; Spaniol et al., 2009). Moreover, some structures activated during this task were previously found to be involved in both language and memory tasks. For example, the temporo-polar cortex, lateral orbitofrontal, and angular gyrus make up a part of the PMAT memory systems (Ranganath & Ritchey, 2012), while at the same time being involved in language networks and engaged in semantic processing (Duffau et al., 2014; Price, 2012).

Additionally, the occipitotemporal, parietal, and hippocampal RA activations match the suggested subsystem representing the link between internal representations and episodic memory (Binder & Desai, 2011; Vandenberghe et al., 2013). This again supports the idea of a large language-and-memory network and shows that these regions are activated when the individual is engaged in mixed language-and-memory tasks and situations. The supplementary analysis comparing RA and GE tasks further suggests that the RA task did not rely exclusively on language processes. Compared to sentence generation and implicit encoding, recalling and repeating that sentence engaged additional parts of the memory network, such as lateral and medial parietal cortices and



hippocampal structures involved in recollection. Specifically, the medial parietal region was proposed to be the interface between the semantic and the hippocampal memory system (Binder & Desai, 2011). On the other hand, the hippocampus was proposed to be the integrator between AT and PM memory systems (Cooper & Ritchey, 2019; Reagh & Ranganath, 2018), and more generally, the interface between language and memory (Covington & Duff, 2016; Pu et al., 2020).

Even though left activation of the hippocampus is expected during this task due to the verbal nature of the material (Limotai & Mirsattari, 2012; Witt et al., 2019), we observed the right activation of this structure during the RA task. One potential explanation could be that participants performed the visual RECO task just before doing the RA task. Namely, participants could have linked the images of the words they saw in the RECO task with the sentences they have generated during the GE task about the same words. Therefore, during the RA task, they did not retrieve just the phrases they produced during the first task. Still, they recalled integrated vivid episodes that also included the images seen in the second task. Due to this, their episodes had a strong visual aspect. That would explain the activation of the right hippocampus that is engaged in perceptual episodic memory (St-Laurent et al., 2016). This could likewise reflect the strategy of relying mainly on visual aspects of the episode during the recall. An alternative explication was proposed by Pu et al. (2020). These authors also observed only the right hippocampal theta response associated with lexical-semantic processing during sentence reading. Pu et al. (2020) suggested that this right activation is related to word concreteness. Their explanation could also apply to our results since all the words were highly concrete as they were presented in the images.

#### 2.4.4 Hippocampal activation

There are two reasons why it is essential for this work to robustly and meaningfully activate the hippocampus. First, it is one of the regions that function as a connector between different parts of the LMN network. Second, hippocampal atrophy often accompanies TLE with implications on language and memory (Alessio et al., 2006; Bonelli et al., 2011; Davies et al., 1998; Zalonis et al., 2017). We have seen that all three tasks we used managed to activate this and its neighboring structures during encoding and recognition memory processes. These findings suggest that the employed strategies of enhancing hippocampal activation by modality change (Perrone-Bertolotti et al., 2015) and increasing protocol sensitivity by including both encoding and retrieval (Buck & Sidhu, 2020) were effective both on the group and individual levels (see Figures 2.2 and 2.3).

As mentioned in Chapter 1, functional differences across the anterior-posterior hippocampal axis have been related to encoding-retrieval processes, specificity, and conceptual/autobiographical-spatial nature of the information (Irish & Vatansever, 2020; Poppenk et al., 2013; Reagh & Ranganath, 2018; Spaniol et al., 2009). Our study design and findings only permitted us to observe the encoding-retrieval specialization regarding the anterior-posterior hippocampal functional differences in concordance to previous studies (Spaniol et al., 2009) even though studies are suggesting that encoding activity can be observed along the entire hippocampal long axis (Poppenk et al.,

2013). Nevertheless, the posterior activation found during retrieval tasks (both RECO and RA) could indeed be linked to retrieval of specific details such as a specific word or a sentence (instead of more global and general information supported by the anterior hippocampus, Irish & Vatansever, 2020; Poppenk et al., 2013; Reagh & Ranganath, 2018).

Although the hippocampus was proposed to be included in the language network (Covington & Duff, 2016), we observed its activation only during the sentence task (GE) when focusing on the difference between correctly and incorrectly encoded items. This finding corresponds well with the recent study that did not find evidence of direct and necessary hippocampal engagement in lexical-semantic processes (Brown-Schmidt et al., 2021). Nevertheless, our findings do not refute the implication of the hippocampus in language processes since there are several explanations for the lack of activations. First of all, it could be that the hippocampus is implied in other aspects of language processing that we have not included in the GE task, such as sentence comprehension (Piai et al., 2016; Pu et al., 2020). It was indeed active during picture naming that we assume the participants were performing during the RECO task. However, we cannot distinguish between retrieval- and naming-related activation. Secondly, it was proposed that comprehension of familiar words (such as those used in our protocol) activate nodes that have already formed connections, so there is no need for new connection formation and hippocampal activity (MacKay et al., 1998). Finally, our results could also suggest that the hippocampus is perhaps not a primary element of the exclusive language network but that it is instead a part of the language-and-memory network, connecting the two systems.

### 2.4.5 Study Limitations

The work presented in this chapter has several limitations. First, due to covert speech, participants' responses for the GE and RA tasks cannot be recorded, and performance on these tasks cannot be measured. Nevertheless, as previous studies employing the covert instead of overt response modality (Benjamin et al., 2017; Haag & Bonelli, 2013), we also identified expected cognitive networks. The solution for future studies using this protocol could be to repeat the recall task outside the scanner (Buck & Sidhu, 2020). This supplementary inquiry would allow testing if participants indeed recalled the sentences. Moreover, it would allow examining the strategy participants used for sentence generation. In other words, it would provide us with the information if the participants generated sentences based on semantic (e.g., A hammer is a tool.) or episodic information (e.g., I bought a hammer two weeks ago.). This information would further help to interpret the obtained maps, especially on the individual level. Secondly, although above the chance level, participants' responses during RECO were not as highly accurate as expected (Perrone-Bertolotti et al., 2015). This could be the consequence of the instructions, as participants were not explicitly instructed to memorize the items they heard during GE. Moreover, this result could have also been influenced by the quality of sound during the GE task. Namely, some of the participants reported that they did not understand all the words. Future studies should work on sound amelioration, although the available equipment primarily limits it. However, the absence of high correctness of the responses allowed us to avoid the ceiling effect

as advised by Buck and Sidhu (2020). Importantly, this also permitted us to compare correct and incorrect responses (Buck & Sidhu, 2020). Although implicit encoding has a high ecological validity (Helmstaedter et al., 1998; Strandberg et al., 2017), a future study should compare the present GE task with the one in which participants would be instructed to try and memorize the items. It should be evaluated if this modification indeed increases the percentage of the correct responses during the RECO task and recalled sentences during RA and whether it increases the activation of the mesial temporal structures. An additional reason to include implicit instead of explicit encoding was to avoid the anxiety it might induce in patients (Petrovich Brennan, 2008). If the version of the GE task with explicit encoding indeed replaces the existing one, the instructions for patients should be carefully designed to avoid causing distress to patients (which could influence the MR signal and results, Benjamin et al., 2018).

It would be very informative to test the language and memory interaction when one of the two is severely damaged, like in patients with amnesia (e.g., Hilverman et al., 2017; Kurczek & Duff, 2011). However, the usage of this protocol demands a certain level of function perseveration which limits its application for some pathologies. For instance, GE2REC would have limited application in patients with Alzheimer's disease (Montembeault et al., 2019) or severe cases of aphasia. However, an adaptation of the protocol could be made in which patients (those able to) would learn some easy phrases before the testing and then only perform the RA task in the scanner. Of course, comparing patients with different disorders using modified protocol versions would be limited. However, it would enable us to explore the effects of different disorders on the reorganization of the language-memory interaction.

Regarding the clinical application, the GE2REC protocol should mainly be used for temporal and frontal epilepsy patients. It should be used with precaution for patients with EZ or lesions in parietal regions, especially SMG, as we did not identify the activation in this region. Nevertheless, this protocol was indeed designed to be used mainly with TLE patients. A modification for these patients could also be made in which they would be explicitly instructed to rely on semantic information when generating phrases. This way, we would force the engagement of the semantic network.

Finally, since we were interested in the language-memory interaction and not the exhaustive individual assessment of these functions, there are many processes that we do not specifically focus on or engage in using this protocol. For instance, we do not evaluate sentence comprehension, which we could also assume is related to the interaction of these two functions (Pu et al., 2020). Indeed it would be informative to test the difference in language-memory interaction during sentence generation and sentence comprehension.

The mentioned suggestions for modifying the protocol would allow exploring additional aspects of the relationship between language and memory. Nevertheless, the current version of the GE2REC protocol was developed regarding the research interest of the REORG project and the need for a protocol that would engage this interaction and be appropriate in both experimental and clinical settings.

## 2.4.6 Conclusion - the LMN that can be mapped with GE2REC

Overall, the vast network (see Box 2.2) recruited by the GE2REC protocol can be considered the interactive language-and-memory network since it was obtained through the linked tasks in which two processes were highly intertwined<sup>5</sup>. It is also important to note that this cerebral substrate of combined and intermixed language and memory processes has specific anatomical support. Specifically, the mesial temporal, temporal pole and prefrontal cortices could be interconnected via the direct inter-hippocampal pathway. In contrast, the polysynaptic pathway could connect parietal and temporal cortices through the parahippocampal gyrus towards cingulate cortices (Duvernoy et al., 2013). Additionally, anterior temporal and orbitofrontal areas that have been found during RA could be connected via UF that supports both functions (Diehl et al., 2008; Duffau et al., 2009; McDonald, Ahmadi, et al., 2008). IFOF could connect frontal and occipital regions, supporting semantic processing, verbal memory, and noetic consciousness (McDonald, Ahmadi, et al., 2008; Moritz-Gasser et al., 2013). Nevertheless, one of the following steps of this line of research will be to explore structural and functional connectivity within the GE2REC language-and-memory network.

We can hypothesize the process flow and functional interaction during each task based on the obtained results. Our findings lead us to the assumption that the following process flow takes place during the GE task: participants hear a word, they perform word recognition (evidenced through activation of pSTG), lexico-semantic search (pMFC, pOrb, pTri, MTG, TP), and syntactic processing (posterior IFG and posterior MTG), while there is a covert speech production (vPMC, vSMC, SMA) that is inhibited (anterior cingulum). Simultaneously, this episode's verbal, visual, and contextual elements are being bound into a coherent event representation (medial temporal structures). In this task, we did not find a more evident activation of parietal regions, which could be explained by the employed contrasts (not highlighting phonologic or pure semantic processing) and memory processes (encoding rather than retrieval) elicited by this task. During the RECO task, the object's name is found through the engagement of regions in the ventral "what" path (occipital, inferior occipitotemporal, inferior parietal, inferior frontal gyrus). The part of this path (lateral orbitofrontal and occipitotemporal) also constitutes the AT memory system. At the same time, since participants are instructed to remember if they heard the word during the previous task, they construct the "GE task" situation (lying in the scanner listening to words). The regions of the PM network (parahippocampus, parietal, and thalamus) could be providing this contextual scaffold (Reagh & Ranganath, 2018). If the retrieval cue (recognized word) activates the representation sufficiently, the hippocampus performs pattern competition, and the representation of the event is brought to the active state. Finally, the findings align with the hypothesis that participants' process flow combines the flows seen in the previous two tasks during the RA task. Therefore, we assume that participants hear a word and perform word recognition (pSTG) and lexico-semantic search (pMFC, pOrb, pTri, MTG, TP). Again, in line with the instruction, participants think of the "GE task" context supported by the PM memory system regions (posterior medial and lateral parietal). The cue (word) activates the representation, and the hippocampus performs

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<sup>5</sup>In Chapter 3, we compare the LMN found in healthy participants and TLE patients with the LMN obtained with the Neurosynth database. These results are not presented here to avoid repetition.

pattern completion (in this case, the sentence). That reactivates syntactic processing (posterior IFG and posterior MTG) and covert production (vPMC, vSMC, SMA, anterior cingulum). Nevertheless, the aforementioned represents only a hypothesis. Mapping of the LMN regions does not provide information concerning their functional dynamics. We would need to test the communication between these regions or their functional connectivity to test these hypotheses.

The obtained findings encourage the assumption that the GE2REC protocol may help explore language-memory interaction in the clinical setting with potential practical benefits. First, its short scan and relatively easy tasks permit mapping language and memory networks and their joint cooperative network. Secondly, previous studies on mapping the neural overlap between cognitive processes pointed out that group-level activations are not necessarily found on the individual level (Seghier & Price, 2016), especially in the case of mesial temporal structures (Saddiki et al., 2018). This protocol increases the access to mesial temporal structures, crucial for preoperative planning, by encompassing two recollecting memory tasks in different modalities. Nevertheless, to support these claims, we need to test if this protocol can map the LMN in TLE patients and be sensitive enough to identify the differences in LMN functioning between these patients and healthy individuals. Such a study could help us better understand this neurocognitive functional interaction and how each function potentially contributes to a specific cognitive deficit. The practical benefits of such knowledge could be greater accuracy and precision when predicting postoperative cognitive deficits and developing neuro-rehabilitation tools to improve a given function (language, for instance) by reinforcing the function it interacts with (such as memory).

Therefore, in the next chapter, we will investigate whether we can map LMN using this protocol in TLE patients and how this network differs between them and healthy individuals.

**Box 2.3 Main conclusions and open questions**

- Main conclusions
  - Using tasks that demand language-memory interaction, we can indeed map LMN. An extensive fronto-temporo-parietal network supports language-memory interaction.
  - LMN network is dynamic as its activation changes based on the task demands (i.e., activation maps varied across GE2REC tasks).
  - We did not find evidence for direct hippocampal implication in language processes; instead, it seems to be binding the elements into a coherent experience during encoding and retrieval.
  - When LMN is engaged in retrieval processes, it employs more posterior parietal regions.
- Open questions
  - Can this protocol activate LMN in patients equally well?
  - What are the differences in the functioning of the LMN in healthy individuals and TLE patients?
  - What are the functional dynamics of the regions that constitute the LMN?

## Chapter 3

# Mapping LMN in Temporal lobe epilepsy patients

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This Chapter is based on the paper Banjac, S., Roger, E., Cousin, E., Mosca, C., Minotti, L., Krainik, A., Kahane, P., & Baciau, M. (2021). Mapping of language-and-memory networks in patients with temporal lobe epilepsy by using the GE2REC protocol. Manuscript under revision for publication.

## 3.1 Introduction

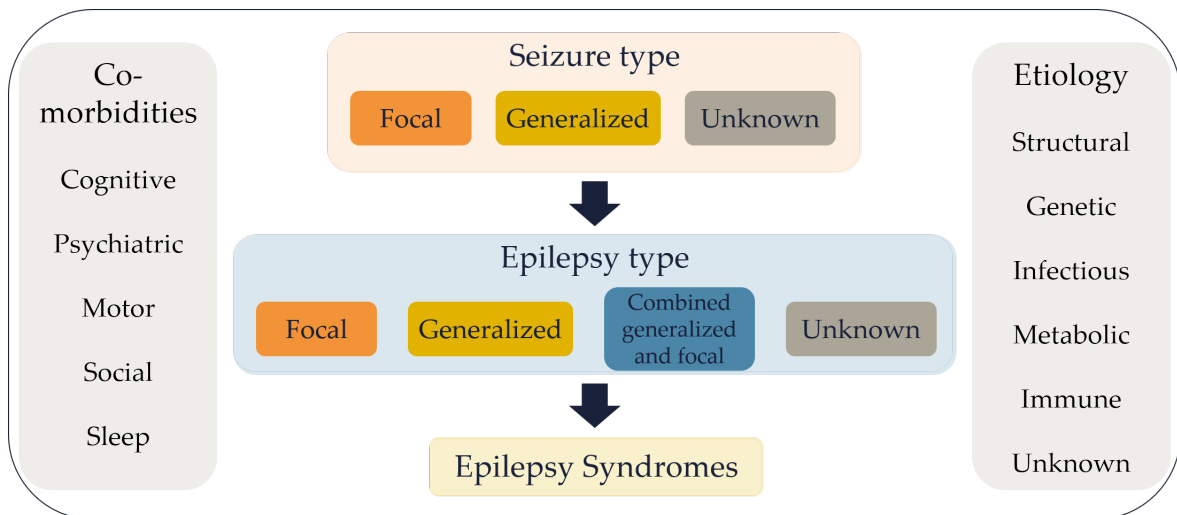
In the previous chapters, we presented the evidence of and discussed language-memory interaction. Moreover, we proposed a way to map the interplay between these functions. Chapter 1 briefly introduced the idea of TLE as a model for studying language-memory interaction. In this Chapter, we will present this neurological disorder in more detail, and then we will try to map LMN in these patients by using the previously shown protocol.

### 3.1.1 What is epilepsy?

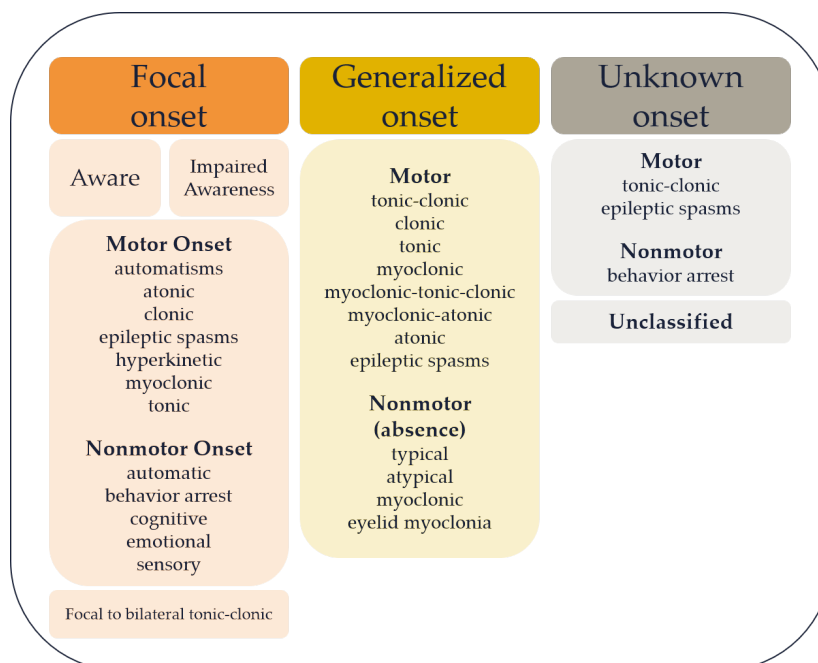
Epilepsy comprises many different diseases and conditions, with seizures as a common element (Fisher, Acevedo, et al., 2014; Scharfman, 2015). A patient with epilepsy encounters recurrent seizures over a certain period (Schoenberg et al., 2011). The term epileptic seizure refers to the transient occurrence of signs caused by abnormal excessive or synchronous electrical discharges of neurons (see Addendum 3.1 for more details on seizures, Fisher et al., 2017). Its variability motivated the classification of the epilepsies and seizure types proposed by the International League Against Epilepsy (ILAE, Fisher et al., 2017; Scheffer et al., 2017). These classifications can guide understanding an individual patient's epilepsy, its triggers, prognosis, risks of comorbidities, and the appropriate antiepileptic therapy.

The epilepsy diagnosis is based on seizure type, epilepsy type, and epilepsy syndromes (see Panel A of Figure 3.1). Two main clinical types of seizures are generalized and focal seizures (although a seizure can have an unknown onset, see 3.1, Fisher et al., 2017). There is also evidence that seizure phenomena should be treated as a spectrum (Kramer & Cash, 2012). The general seizures involve, as their name suggests, all or significant portions of the brain. On the other hand, in focal seizures, abnormal neural activity starts as a local event or activity that spreads by engaging other pathological and healthy brain areas (Barr, 2015; Kramer & Cash, 2012). Focal epilepsy affects around 60% of epilepsy patients (Télez-Zenteno & Hernández-Ronquillo, 2012). Focal seizures can be further characterized based on whether the awareness is retained (previously known as the “simple partial seizure”) or not (previous “complex partial seizure”). These seizures can also be categorized based on the presence of motor and nonmotor symptoms at the onset. Epilepsy syndrome (e.g., childhood absence epilepsy, West syndrome, and Dravet syndrome) presents a group of characteristics such as seizure types, EEG, and imaging features that often happen together that can be related to certain comorbidities (intellectual and psychiatric dysfunction) and can have etiologic, prognostic and treatment indications (Fisher et al., 2017; Scheffer et al., 2017).





(A) Epilepsy classification framework proposed by ILAE



(B) Operational seizure type classification proposed by ILAE

**Figure 3.1:** Classification of epilepsies and seizures proposed by ILAE (A) Framework proposed by Scheffer et al. (2017) for classification of the epilepsies. The seizure types criteria refer to seizure onset presented on Panel B. (B) Operational classification of seizure types proposed by Fisher et al. (2017).

### From epileptogenic zone to epileptogenic network

Epileptic network refers to the brain area of altered tissue engaged in a focal seizure (Blumenfeld, 2014; de Curtis & Avoli, 2015). Generally, contemporary research suggests that we should move from conceptualizing epilepsy as a symptom of localized abnormalities and perceive it as a network disorder concerning the organization of epileptic regions, seizure propagation, and brain networks modification (Kramer & Cash, 2012; Smith & Schevon, 2016). Within this framework, it was proposed that

these epileptogenic networks are hierarchical (Bartolomei et al., 2017). The epileptogenic zone network consists of brain regions capable of seizure generation through fast activities. This network shows a synchrony-desynchrony pattern. Seizure onset is characterized by a decrease in synchrony between the engaged structures. However, epileptic manifestation cannot be accredited only to epileptogenic focus (Khateb et al., 2021). The seizure within these regions triggers the less epileptogenic areas that form a propagation zone network and show lower frequency and higher synchronization. The synchronization within the propagation network is thought to be the basis of the clinical symptoms. The areas that do not engage in seizure propagation compose the non-involved network (Bartolomei et al., 2017). These networks show different functional connectivity within and between them. It is higher within epileptogenic and propagation zone networks than in the non-involved network. Also, regions within the epileptogenic zone network show preferential coupling with the regions within this network and to a lesser degree with regions in the propagation network (Lagarde et al., 2018).

### **Possible treatments?**

The most prevailing treatment of epilepsy is administering an antiepileptic medication to suppress seizure generation and propagation (for a recent review of antiepileptic medication, see Khateb et al., 2021). However, they are efficient in approximately 70-65% of cases, while the rest of the patients are pharmacoresistant (Borger, Schneider, et al., 2021; Fattorusso et al., 2021).

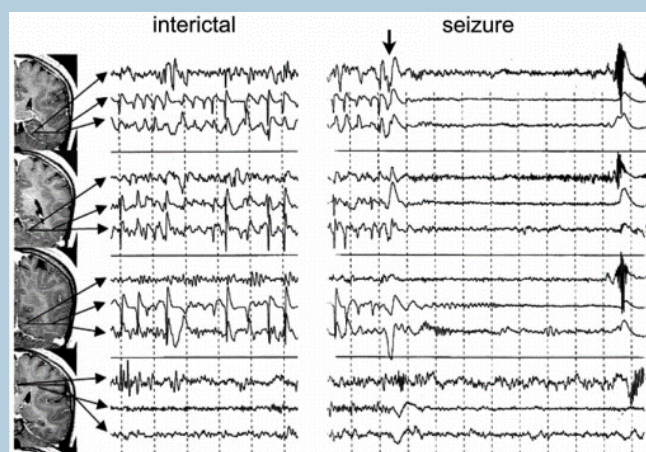
For a patient with epilepsy to be diagnosed as drug-resistant, two trials of tolerated, appropriately chosen, and used antiepileptic medication (one or a combination) have to fail to achieve sustained seizure freedom (Fattorusso et al., 2021; Kwan et al., 2009). The pooled prevalence proportion of pharmacoresistant patients among epilepsy patients is between 0.25 and 0.30 (Kalilani et al., 2018; Xue-Ping et al., 2019). A recent meta-analysis showed that the main risk factors for pharmacoresistant epilepsy are abnormal EEG, status epilepticus, febrile seizures, symptomatic etiology, and the presence of multiple types of seizures (Xue-Ping et al., 2019).

For drug-resistant patients, curative surgery to remove or inactivate the epileptogenic focus remains the only solution to stop seizures (Schoenberg et al., 2011; Téllez-Zenteno et al., 2005). To prevent possible postoperative deficits, rigorous presurgical evaluation is mandatory (Baxendale et al., 2006; Drane & Pedersen, 2019; Sherman et al., 2011). For this evaluation, the nature and characteristics of this type of epilepsy need to be taken into account, as well as the neural reorganization it causes and the concomitant neuropsychological changes. One of the epilepsies that most often show drug resistance is TLE (Jallon et al., 2001; Téllez-Zenteno & Hernández-Ronquillo, 2012), which is of particular interest for this work.

### Addendum 3.1 EEG manifestation of focal epileptic seizures

Various EEG patterns can be identified during a seizure. We will present the main terms and the most consistent pattern (for a review, see de Curtis & Avoli, 2015). A seizure is temporally delimited into several phases. The epileptiform discharges during seizures are termed ictal discharge. The pathological pattern of activity between seizures is called interictal epileptiform discharge and postictal that can be observed after a seizure (see figure below, de Curtis & Avoli, 2015; Scharfman, 2015). Scalp EEG is highly valuable in detecting seizure propagation, while intracranial recordings help locate the epileptogenic region (de Curtis & Avoli, 2015).

The seizure starts as a sudden imbalance between excitatory and inhibitory processes in the neural network. In pathological conditions, such as epilepsy, intrinsic factors can lead to excessive excitability of nerve cells and seizures. Long-term excitation/inhibition imbalance starts the process of epileptogenesis and forming of the epileptogenic network. A seizure happens as excessive bioelectric activity of a group of neurons and hyper-synchronization of this activity across the cortex (Sendrowski & Sobaniec, 2013). The EEG patterns related to seizures are called epileptiform (Fisher, Scharfman, et al., 2014). Focal seizures show a dynamic pattern. They typically start with either low-voltage fast activity (the background activity amplitude decline and start of low-voltage fast activity in beta-gamma range) or “hypersynchronous” potentials (shown as large-amplitude spike potentials). This phase is followed by a large amplitude and irregular spiking pattern, called “tonic” discharge. The synchrony of activity builds up, seen as rhythmic bursting, and there is a clustering of highly synchronous discharges (sometimes called “clonic phase”) followed by electrical depression (de Curtis & Avoli, 2015; Fisher, Scharfman, et al., 2014). However, a desynchronization in the early phases of seizures was also found (de Curtis & Avoli, 2015). The synchronized large-amplitude bursts that occur at the end of a seizure suggest that synchronization could be facilitating seizure termination. This indicates that networks fragmented during seizure onset merge during seizure propagation and then form one dominant component before its ending (Fisher, Scharfman, et al., 2014; Jiruska et al., 2013).



Example of the intracerebral stereo-EEG recording in a patient with focal epilepsy. Going from left to right: position of electrodes, interictal discharges, seizure. Figure adapted from Fisher, Scharfman, et al. (2014)

### 3.1.2 Characteristics of the TLE

The name of the TLE, the most common focal epilepsy in adults (Barr, 2015; Fiest et al., 2017; Téllez-Zenteno & Hernández-Ronquillo, 2012), indicates that the seizures are induced by the epileptogenic network located in temporal regions. Nevertheless, there is growing evidence based on different neuroimaging techniques showing that this type of epilepsy includes network dysfunctions that are not only limited to the ipsilateral temporal lobe. For instance, these patients showed bilateral thinning of the frontal (precentral, paracentral, and pars opercularis to the orbital region) and lateral temporal region, as well as ipsilateral thinning in SMG, MTG, and medial orbital cortex (McDonald, Hagler, et al., 2008). Moreover, TLE patients were found to have global and lobar white matter volume and connectivity anomalies (Otte et al., 2012; Slinger et al., 2016), changes in the superficial white matter (M. Liu et al., 2016) and large-scale functional network disruptions (Liao et al., 2010, see Chapter 4).

TLE is often accompanied by hippocampal sclerosis (HS, see Addendum 3.2), which is sometimes considered as a distinct syndrome of “mesial temporal epilepsy” (Hermann et al., 1997). However, intracerebral electrode studies demonstrated the complexity of temporal lobe epileptogenic networks, making it impossible to reduce them only to HS. Kahane and Bartolomei (2010) suggested considering MTL structures as an epileptogenic network based on depth EEG recordings. They report that the hippocampal onset is found in 20-65% of seizures. The potential seizure generators can also be the amygdala, or amygdalohippocampal complex, the parahippocampal gyrus, and the entorhinal cortex. Therefore they present a spectrum of TLE associated with HS. In addition to the mesial subtype, these authors also distinguish the temporopolar, mesiolateral, lateral, and temporal “plus” TLE subtypes. The epileptogenic network of the last subtype includes the orbitofrontal cortex, insula, frontal and parietal operculum, and the temporo-parietooccipital junction in addition to the temporal lobe (Kahane et al., 2015). Another form of TLE is so-called “MRI-negative TLE”, in which seizures originate from mesial or lateral temporal regions, or it can even be “temporal plus” epilepsy, though there is no observable epileptogenic lesion (Muhlhofer et al., 2017). In temporal lobe seizures, the thalamus was also found to have a critical role, described as seizure amplifier and synchronizer since there was an increased correlation between thalamus and temporal lobe structures during seizures (Bartolomei et al., 2017).

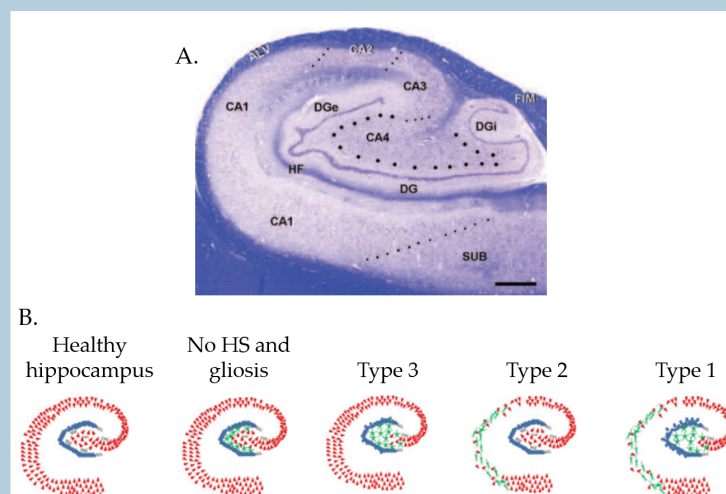
TLE can have different etiology. The most common are HS, infections, tumors, perinatal hypoxia, traumatic brain injury, vascular anomalies, genetic influences, and cryptogenic (Thomas et al., 2019). A typical course of TLE with HS starts with prolonged febrile seizures in early childhood followed by several years without the seizures (a latency period of 5-10 years) that begin in mid-to-late childhood as focal seizures manifested as isolated auras without loss of awareness. During adolescence and early adulthood, there could be periods of seizure remission that can be medically controlled. With the illness progression, seizures become elaborate and treatment-resistant with accompanying cognitive difficulties (O’Dell et al., 2012; Thomas et al., 2019).

### Addendum 3.2 Hippocampal sclerosis

Hippocampal neurons are vulnerable to various insults (e.g., hypoxia, hyperglycemia, stress, etc.), and it plays a role in multiple neurodegenerative disease processes (Thom & Bertram, 2012). This structure shows high plasticity in terms of neurogenesis and function (Lemaire et al., 2012; Toda & Gage, 2018). And it was proposed that its high plasticity and high vulnerability are linked (McEwen, 1994).

HS is the most common histopathologic anomaly associated with drug-resistant TLE (Blümcke et al., 2013). However, it is not a unique phenomenon, and there are different patterns of cell loss within hippocampal subfields. Nevertheless, the hallmark of HS is the loss of segmental pyramidal cells (Hamelin & Depaulis, 2015). In general, ILAE classification distinguishes two main groups - typical (type I) and atypical (type II and III) HS based on patterns of nerve loss and gliosis (see figure below). Type I HS, the most frequently observed type, is characterized by pyramidal cell loss in CA4 and CA1 sectors, while CA3, CA2, and dentate gyrus damage are more variable. Type 2 shows predominant neuronal cell loss in CA 1. Type 3 involves cell loss, mainly in CA4. Type 4 shows no HS and gliosis (Blümcke et al., 2013; Walker, 2015). This classification is informative for surgery planning since Type 4 and 2 have the poorest outcome (approximately 40% seizure-free patients). In comparison, Type 1 shows the best postsurgical results (about 70%) (Walker, 2015, see Chapter 5 for discussion about surgery outcomes). HS is more frequently observed accompanied by a secondary lesion than isolated (Gales et al., 2017). It was shown that different hippocampal regions show different susceptibilities for epileptiform activity. However, this activity can be induced in different areas, including those characterized by severe neuronal loss (Reyes-Garcia et al., 2018).

The hippocampus is especially vulnerable to damage caused by seizures. Patients with HS often experience febrile or prolonged seizures in their childhood. As the additional possible causes of HS, studies report head injuries, genetic predisposition, underlying maldevelopment of this structure, infections, as well as more severe cortical and vascular malformations, and low-grade glioneuronal tumors (Walker, 2015). The “two-hit” hypothesis suggests that mesial TLE and HS develop due to the association of different “hits” or factors such as febrile seizures, genetic background, brain lesions, dysplasia, encephalitis, depression, stress, or sleep apnea. The insults in the immature brain (such as seizures) make the mature brain more prone to later seizure-induced injuries (Hamelin & Depaulis, 2015).



A. Anatomy of the hippocampus. SUB = subiculum; DG = dentate gyrus. Figure taken from Blümcke et al. (2013). B. Schematic illustration of the ILAE classification. Red = pyramidal neurons; blue = granule cells; green = astrocytosis. Figure adapted from Thom (2014).

The seizures that originate from temporal or limbic zones last between 90 and 120s. They typically begin with auras with visceral sensation. These seizures are also usually characterized by epigastric discomfort (most specific for mesial temporal onset), alteration of awareness, behavior arrest, and signs such as fullness of the face, flushing, arrest of respiration, olfactory-gustatory hallucinations (Browne & Holmes, 2008; Thom & Bertram, 2012; Thomas et al., 2019). At the onset, patients show partial awareness, followed by its loss, motionless stare, and (oro-alimentary, vocal, or gestural) automatisms. TLE seizures also include cognitive and emotional changes that can manifest in behavior. Those originating from the hippocampus are usually characterized by memory phenomena such as *déjà vu* and an emotional component if the amygdala is included (Barr, 2015). If the origin of temporal seizure is more lateral, patients will experience auras with illusory auditory or visual phenomena and possible language disorders (Browne & Holmes, 2008). Postictal confusion, headache, and language disturbance often follow the termination of TLE seizures (Thomas et al., 2019).

### 3.1.3 Cortical reorganization following TLE

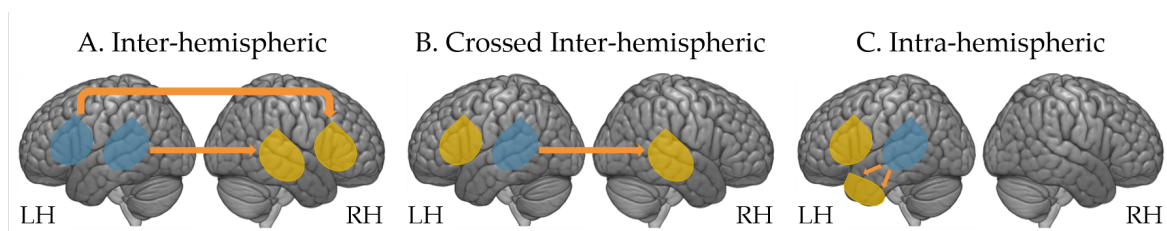
One of the essential characteristics of the brain is that it does not have a static functional organization. Cerebral plasticity is a continuous process that allows short, middle, and long-term remodeling of neural networks to optimize their functioning (Duffau, 2006). This process acts during phylogenesis and ontogenesis but also in the case of brain insult. For instance, atypical language representation is more prevalent in epilepsy patients (24.5%) than in healthy individuals (2.5%) (Berl et al., 2014; Goldmann & Golby, 2005). TLE patients show variable probability and degree of cerebral reorganization of language and memory networks at inter- and intra-hemispheric levels (Baciu & Perrone-Bertolotti, 2015; Chang et al., 2017; M. K. Sidhu et al., 2013) that can have a double origin, chronic epilepsy, and surgery. This chapter will focus on the TLE-induced reorganization of task-based activation, while Chapter 4 will focus on reorganization in terms of functional connectivity.

There are several mechanisms of brain neuroplasticity that can be manifested as different patterns of reorganization identified in TLE patients (Baciu & Perrone-Bertolotti, 2015; Duffau, 2006). Brain areas supporting a specific function are dynamically organized and exhibit “cortical redundancies” (multiple representations of the same function within the same region). Therefore brain damage of a site can be followed by recruitment of the adjacent redundant site (Duffau, 2006). However, in severe lesions, redistribution within the same area is not enough to maintain the function. Therefore, other regions within the functional network are recruited. For instance, when the hippocampus is damaged, a compensatory mechanism for memory retrieval can modify an existing memory network by generating a bypass network, including the other memory regions such as the medial retrosplenial cortex, posterior cingulate, and mPFC (Limotai et al., 2018).

In general, three main types of reorganization are identified, especially concerning language function (Baciu & Perrone-Bertolotti, 2015; Balter et al., 2019, see Figure 3.2). Although relying on the data-driven clustering method, Berl et al. (2014) found 15 possible patterns of language representations in epilepsy patients. Nevertheless, these

three general patterns summarize and present the main findings regarding language and memory reorganization in TLE patients.

The first, inter-hemispheric reorganization manifests as a “shift” of the typical left language networks to their right homologs (Panel A, Figure 3.2 Baciú & Perrone-Bertolotti, 2015; Balter et al., 2019). It could be associated with removing or reducing the transcallosal inhibition that is usually responsible for the LH dominance (Baciú & Perrone-Bertolotti, 2015; Tzourio-Mazoyer et al., 2017). In the case of memory, patients with unilateral TLE with HS show reduced ipsilateral and increased contralateral activation during various encoding tasks (Golby et al., 2002; Powell et al., 2007).



**Figure 3.2:** Typical patterns of cortical reorganization in TLE. These patterns present the most common language reorganization patterns, but the principle is also applicable to memory reorganization. (A) The inter-hemispheric pattern is observed when regions engaged in language move from the dominant (LH) to the non-dominant hemisphere (RH). (B) In the crossed inter-hemispheric pattern, only some regions shift to the non-dominant hemisphere (RH). (C) The intra-hemispheric pattern represents the recruitment of other regions within the injured dominant hemisphere. LH = left hemisphere, RH = right hemisphere. The figure is adapted from Baciú and Perrone-Bertolotti (2015)

The second crossed inter-hemispheric reorganization is manifested as a partial “shift” of the typical language regions to the right hemisphere (Panel B, Figure 3.2 Baciú & Perrone-Bertolotti, 2015; Balter et al., 2019). For instance, frontal regions that are part of the production network might be right-lateralized, while the temporal regions of the semantic network can be right-lateralized (Balter et al., 2019). This pattern might also indicate a regional dissociation between different language processes (Tzourio-Mazoyer et al., 2017). It was proposed that if the epileptogenic zone is in the dominant hemisphere, in the proximity of a region engaged in language, the inter-hemispheric inhibition is reduced, leading to the increased engagement of the homologous region in the non-dominant hemisphere (Baciú & Perrone-Bertolotti, 2015; Tzourio-Mazoyer et al., 2017). In the case of memory, TLE patients can show the activation of the contralateral hippocampus and ipsilateral parahippocampal gyrus during the memory recognition task (Banks et al., 2012).

If the damage affects multiple centers within a functional network, then the structures outside of the network are engaged. When the unimodal association areas within a network are damaged and therefore cannot help in functional restoration, a compensatory strategy consists of heteromodal association areas replacing these unimodal association areas (Duffau, 2006). This mechanism can be observed in the third, intra-hemispheric reorganization consists of the recruitment of regions in the dominant hemisphere, initially non-specialized for language or memory (Panel C, Figure 3.2 Baciú & Perrone-Bertolotti, 2015; Cousin et al., 2008). For memory function, TLE patients with HS can also show elaborate compensatory reorganization that includes both temporal and

extra-temporal structures (Guedj et al., 2011; M. K. Sidhu et al., 2013).

An essential aspect of reorganization is its efficiency. An efficient pattern of reorganization indicates that brain restructuring is associated with typical cognitive performance. The reorganization pattern a TLE patient will develop and its efficiency can depend on numerous factors. In the case of language, it was shown that the inter-hemispheric organization of the language network was more associated with early ASO, HS, and epileptogenic zone in the hemisphere specialized for language (Baciu & Perrone-Bertolotti, 2015). For instance, HS was associated with the altered functional organization of lexical and semantic networks in TLE patients (Jensen et al., 2011). Moreover, the atypical speech dominance was more frequent when left HS was present than right (Janszky, 2003). Similarly, ASO, epilepsy duration, and seizure frequency influenced memory encoding in TLE patients (M. Sidhu et al., 2015).

Nevertheless, these variables can also interact. For instance, a patient with early ASO and epileptogenic zone in the dominant hemisphere can show inter-hemispheric reorganization. This change can be fast and efficient due to strong synaptic plasticity and less rigid inhibitory mechanisms at a younger age. For the same reasons, inter-hemispheric reorganization in a patient with a late ASO can result in poorer language functioning. Therefore, supplementary ipsilateral and peri-lesional regions can also be engaged as a compensatory strategy (Tzourio-Mazoyer et al., 2017). There is also evidence that temporal regions are more prone to inter-hemispheric language reorganization than frontal (Perrone-Bertolotti et al., 2012; Thornton et al., 2016). Regarding memory, the contra-lateral MTL reorganization during encoding was related to poorer functioning (Powell et al., 2007), while longer epilepsy duration and seizure frequency were related to contralateral extra-temporal memory reorganization, which was not efficient (M. Sidhu et al., 2015). As aforementioned, these epileptic insults of temporal regions forming language and memory networks, and their reorganization manifest in the cognitive functioning of TLE patients. We will now present the main findings regarding the neuropsychological functioning of these patients.

### 3.1.4 Neuropsychology of temporal lobe epilepsy

As we saw in Chapter 1, language and memory networks converge towards integrative hubs in the left temporal lobe. Therefore, although intellectual capacities are usually intact in TLE patients, they typically show language and memory deficits, even more so if their epileptogenic network is mesially focused (Perrone-Bertolotti et al., 2012; Phuong et al., 2020; Zalonis et al., 2017).

In 30-60% of left TLE (LTLE) patients, the verbal memory declines (Bell et al., 2011), as well as long-term memory (Tramoni-Negre et al., 2017). TLE patients with HS also have poorer episodic memory and executive functions than those without it (Phuong et al., 2020). At the same time, studies suggest that between 40 and 55% of patients with LTLE and 36% of those with right TLE (RTLE) show naming deficits (Bartha-Doering & Trinka, 2014; Zhao et al., 2014). Additionally, TLE patients with HS have worse naming performance than those without it (Davies et al., 1998), and the volume of the left hippocampus significantly predicts verbal fluency and naming (Alessio et al., 2006). It was recently shown that language and memory tests combined were the most relevant in segregating left and right mesial TLE patients (Roger, Torlay, et al., 2020).



There have been proposals for grouping TLE patients with similar profiles of cognitive functions to advance the comprehension of the neuropsychological complications that follow this neurological disorder (Hermann et al., 2007). One of the most recent taxonomies was provided by Reyes et al. (2020). These authors found three profiles: TLE patients with intact cognition, those with verbal memory and language impairments, and those with generalized impairment. Moreover, it was shown the segregation between cognitive domains is lower in individuals with TLE (Kellermann et al., 2016). These patients show a higher alliance between cognitive domains, suggesting a compensatory mechanism for cognitive difficulties.

These TLE comorbid cognitive difficulties are associated with the cause, ASO, seizure frequency, education, and antiepileptic drugs (Kanner et al., 2020; Phuong et al., 2020). However, epilepsy patients were also found to experience cognitive difficulties even before starting the pharmacologic treatment (Taylor et al., 2010). TLE patients also show different cognitive trajectories from healthy individuals over a more extended period (4 years) (Hermann et al., 2006). The lateralization of the epileptogenic zone is also an important factor for the characteristics and severity of neuropsychological impairment. Although RTLE patients encounter language and memory difficulties, they are more severe in patients with LTLE (Alessio et al., 2006; Roger, Torlay, et al., 2020). Nevertheless, Phuong et al. (2020) recently found that left TLE patients only showed poorer verbal memory abilities than right TLE, while there was no difference in language abilities.

### 3.1.5 Why should we study language-memory interaction in TLE?

After this short overview<sup>1</sup>, it is clear that TLE impacts the quality of life and can have a significant economic impact on a patient and society (Scharfman, 2015). For instance, Kobau et al. (2017) found that only 52% and 54% of epilepsy patients report good physical and mental health, respectively, which was significantly less than people with other diseases (e.g., heart disease, cancer, or hypertension). We saw that if a person cannot be relieved of the burden of seizures with medication, surgery remains a potential solution. This scenario is especially prevalent in TLE patients. However, the operation's goal is to avoid a further cognitive decline in addition to seizure relief. As temporal regions are crucial for language and memory, surgery in these regions must be preceded by detailed preoperative mapping of these functions to avoid possible postoperative deficits (Baxendale et al., 2006; Drane & Pedersen, 2019; Sherman et al., 2011). Based on previously presented information, we conclude that language and memory mechanisms and substrates are highly interconnected. Therefore, the first answer to the question in the subtitle is to provide a more comprehensive presurgical mapping of cerebral representations of language and memory that incorporates contemporary

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<sup>1</sup>The presented review is not exhaustive. TLE, and epilepsies in general, are highly complex disorders that can be studied from different fields and frameworks. A more detailed elaboration of each of the presented aspects of TLE would surpass the scope of this work. This introduction aimed to depict a general picture of TLE, focusing on those aspects that are of importance for this work. Further information can be found in Wasade and Spanaki (2019) and Barr and Morrison (2015), while Valeta (2017) provides an epilepsy guidebook for patients.

understandings of cognitive functions. That should allow for a better understanding of the cerebral substrates and the basis of the patient's cognitive functioning as revealed by neuropsychological assessment. Furthermore, this perspective should also indicate how patient's cerebral networks are reorganized to support the function. This information is crucial not only for surgery planning but also for prehabilitation and cognitive rehabilitation.

On the other hand, the fact that TLE patients also encounter language difficulties in addition to the expected memory deficits opened numerous research questions. There are indeed several hypotheses regarding why and how TLE would affect the language. It was proposed that poorer language functioning is a result of the overlap between the epileptogenic and language network, which only concerns TLE patients but not those with mesial TLE (Phuong et al., 2020). The epileptic burden would indeed prevent the proper functioning of the regions within the language network. However, findings on language difficulties in mesial TLE patients (Davies et al., 1998) and the association between hippocampal volume and naming (Alessio et al., 2006) partially refute this hypothesis. The other proposed hypothesis is that the hippocampus engages in semantic tasks (Phuong et al., 2020). Studies in TLE patients indeed indicated the hippocampal role in role retrieval during naming, fluency, and lexical-semantic aspects of sentence processing (Bonelli et al., 2011; Hamamé et al., 2014; Piai et al., 2016; Pu et al., 2020). However, a recent study did not find evidence for direct and necessary hippocampal implication in lexical-semantic mappings (Brown-Schmidt et al., 2021). The study presented in Chapter 2 also did not find hippocampal engagement when focusing on the language task, suggesting that this structure may not be a primary element of the language network but an integrator between language-and-memory network. Another proposed hypothesis about language difficulties in TLE is the effects of confounding factors such as antiepileptic drugs (Phuong et al., 2020). Although these medications can have this effect, TLE patients can show cognitive deficits even before starting the treatment or even before the onset of the seizures (Kanner et al., 2020; Taylor & Baker, 2010). Finally, Baciú and Perrone-Bertolotti (2015) proposed that during language left hippocampus inhibits the right one and facilitates the activity of left hemisphere language regions, which, in turn, inhibits the activity of contralateral regions. In the case of HS, the left hippocampus might not exert these influences leading to higher excitatory effects of the right hippocampus on the right hemisphere language regions. Although this hypothesis could only explain the inter-hemispherical pattern of reorganization, it suggests the implication of memory regions in cerebral representation and functioning of the language.

Given the abovementioned reasons, we will assess the interactive LMN in TLE patients using the same GE2REC protocol applied in healthy individuals. We will also explore the LMN differences between healthy individuals and those with TLE. Finally, we will evaluate whether the obtained neural representations correlate with neuropsychological performances.

**Box 3.1 Characteristics of Temporal lobe epilepsy**

- TLE is a dynamic neurological disorder affecting neuronal networks.
- Hippocampal sclerosis is often found in TLE patients.
- Temporal lobe epilepsy is often pharmaco-resistant.
- TLE patients show both language and memory deficits.
- Language and memory networks show various patterns of reorganization in TLE patients.
- Reorganizations of language and memory networks are interrelated.
- Comprehensive mapping of language and memory interacting representations is crucial for surgery, prehabilitation, and rehabilitation planning.

## 3.2 Material and Methods

### 3.2.1 Participants

The present study included eighteen LTLE patients candidates for curative surgery (age  $35 \pm 10.9$ ; 10 females; 17 right-handed) and nineteen healthy controls (HC, age  $21.2 \pm 2.97$ ; 8 females; all right-handed) without neurological deficits or psychiatric disease. Patients were diagnosed with drug-resistant LTLE by neurologists based on a synthesis of several evaluations (clinical, scalp/depth-EEG, MRI/PET scan) following the recommendations of the ILAE committee report (Kwan et al., 2009; Scheffer et al., 2017). The Edinburgh Handedness Inventory (Oldfield, 1971) was used to determine handedness in LTLE. All participants were French native speakers with normal or corrected-to-normal vision. One HC participant was excluded from the fMRI analyses due to the high number of data artifacts. For patients, fMRI evaluations were part of their presurgical assessment. Demographic, clinical, and neuropsychological details of all LTLE patients are presented in Tables B.1 and B.2 in Appendix B.

### 3.2.2 Neuropsychological and language assessment in patients

LTLE patients underwent neuropsychological, and language assessments carried out by a neuropsychologist and a speech therapist. The present study used the assessment results to test the cognitive efficiency of obtained cerebral (re)organization. The following cognitive scores were used in the analyses: (a) general cognitive level (IQ) composed of: verbal comprehension index (VCI) (WAIS IV, Wechsler, 2008) (b) language scores: naming (DO80, Deloche & Hannequin, 1997), semantic fluency (SFL), and phonological fluency (PFL, Godefroy & GREFEX, 2008); (c) memory scores: auditory memory index (AMI) and visual memory index (VMI; WMS IV, Wechsler, 2009). Test scores were standardized by gender, age, and sociocultural level based on validation data of each neuropsychological test used.

### 3.2.3 fMRI assessment of language and memory

Participants performed the [GE2REC](#) protocol presented in Chapter 2.

### 3.2.4 MR Acquisition

Acquisition parameters in this study were the same as in the previous study presented in Chapter 2.

### 3.2.5 Data processing

#### Behavioral analyses of the RECO task

Based on the responses during the RECO run, we calculated behavioral performances for the memory recognition task. Statistical analyses were performed using Jamovi statistical software [The jamovi project (2020). jamovi (Version 1.6) Retrieved from <https://www.jamovi.org>]. The Mann–Whitney U test was used to test the differences in the responses between LTLE patients and HC.

#### Functional MRI analyses

**Preprocessing steps.** The preprocessing was performed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/spm/>) running under Matlab R2019b (Mathworks Inc., Natick MA, USA) using the standard routines. All images were realigned to correct the head motion, time-corrected with the mean image as the reference slice, spatially normalized to MNI (Montreal Neurological Institute) space, and then spatially smoothed with an 8 mm FWHM (Full Width at Half Maximum) Gaussian kernel. The T1-weighted anatomical volume was co-registered to the mean image created by the realignment procedure and was normalized within the MNI (Montreal Neurological Institute) space. The anatomical normalization parameters were subsequently used for the normalization of functional volumes. Noise and signal drift was removed by using a high-pass filter (1/128 Hz cutoff). Preprocessed data were then statistically analyzed.

**Functional MRI statistical analyses.** Sentence generation and Recall runs were analyzed as a block design, while Recognition run was analyzed as an event-based design. Statistical parametric maps were generated from linear contrasts between the HRF parameter estimates for the different experimental conditions. The whole-brain effects of interest were firstly evaluated at an individual level (first-level) to assess: (1) effect of language by comparing sentence generation with the baseline; (2) effects of memory recognition by comparing correctly recognized items with the baseline; and (4) effects of memory recall by comparing sentence repetition with the baseline. Six movement parameters obtained by realignment corrections were included as noise (regressors of non-interest).

For the second-level group analyses, individual contrasts were entered into a one-sample t-test, and activations were reported at a  $p < .05$  significance level with the FWE correction ( $T_{GE} > 6.89$  for sentence generation,  $T_{RECO} > 7.03$  for recognition, and

$T_{RA} > 6.85$  for recall task) with a threshold of 5 voxels ( $k > 5$ ) for all effects. However, we also repeated the second-level group analyses at a more permissive threshold ( $p < .001$ , uncorrected) to test if the activation can be identified in regions expected to be engaged in language and memory processing by previous studies and models. An additional reason for threshold lowering is that one of the hub regions of the LMN, the hippocampus, and mesial temporal structures in general, can be affected by geometric distortions and signal loss (Buck & Sidhu, 2020; Haag & Bonelli, 2013; Powell & Duncan, 2005).

The ability of GE2REC to activate expected LMN was assessed by comparing GE2REC activation maps with the maps obtained via Neurosynth for language and memory (Yarkoni et al., 2011) in terms of AAL regions coverage (Tzourio-Mazoyer et al., 2002). The procedure is explained in detail in [Supplementary Material](#) of Chapter 3.

To test differences between LTLE and HC, we performed the same first-level analyses for HC. Then the individual contrasts of LTLE and HC were entered into a two-sample t-test to perform third-level group analyses. Since there was a significant age difference between LTLE and HC, we also added age as a covariate. Considering that the addition of the regressors can decrease statistical power (Lazar, 2008), activations were reported at a lower threshold ( $p < .001$  uncorrected)  $T > 3.35$  for all tasks and a threshold of 5 voxels ( $k > 5$ ).

**Hemispheric lateralization and reorganization.** We assessed the lateralization index (LI) of activations using the bootstrap method of the SPM LI toolbox (Wilke & Lidzba, 2007). This method was chosen because it is threshold-independent, robust, and resistant to outliers. A more detailed overview of methodological issues and solutions regarding the calculation of LI is presented in [Appendix B](#).

We calculated general LIs for frontal and temporal cortices and regions of interest (ROI). The ROI LIs were calculated to evaluate the efficiency of cortical organization and reorganization of TLE patients (see the following subsection). We employed specific ROIs instead of the whole lobe LIs so that the obtained results could be interpreted in terms of specific processes. Although many LMN regions are essential for proper cognitive functioning, we focused on those considered hubs. Specifically, we included inferior frontal orbitalis, triangularis, and opercularis engaged in multiple language processes (e.g., semantic and syntactic) and performing unification and integration (Hagoort, 2016). The middle temporal gyrus was included as a part of the lexico-semantic network (Binder & Desai, 2011; Hertrich et al., 2020; Middlebrooks et al., 2017; Price, 2012), while the inferior parietal cortex was included for its engagement in semantic and control processing (Baldo & Dronkers, 2006; Bzdok et al., 2016; Wen et al., 2018). Finally, the hippocampus was included since it plays a unifying role by binding the features into a coherent representation and supporting flexible cortical retrieval (Cooper & Ritchey, 2019; Ranganath & Ritchey, 2012), and was proposed to be the link between language and memory (Duff & Brown-Schmidt, 2012). ROIs were anatomically defined using the WFU pickatlas toolbox (Maldjian et al., 2003) and the AAL atlas (Tzourio-Mazoyer et al., 2002).

To test the variation in lateralization of specific regions and the potential reorganization according to status (LTLE or HC), we calculated differences in LIs between groups using the Man-Whitney U test and the effects of task and lobe, using the Friedman

test for repeated measurements with Durbin-Conover test for pairwise comparisons. Since the hippocampal region is of particular interest for patients with LTLE, we specifically calculated the difference between LTLE and HC in the distribution of hippocampal lateralization using the Chi-square test. LIs higher than 0.2 were considered left-lateralized, and those below were bilateral-to-right (Seghier, 2008). We grouped bilateral and right lateralization given the reduced number of participants. That way, participants had either left or non-left lateralization.

**The efficiency of language-and-memory (re)organization.** To determine the efficiency of potential reorganization, we correlated the LIs-ROIs with either RECO performances or neuropsychological scores. To explore clinical characteristics associated with possible reorganization, we correlated the LIs with the clinical features of TLE patients. The results were FDR corrected for multiple comparisons.

## 3.3 Results

### 3.3.1 Behavioral results of the RECO task

Overall, LTLE had a lower % of correct responses (%CR) than HC ( $U = 105$ ,  $p = .046$ ) and were slower (RTs) than HC ( $U = 39$ ,  $p < .001$ ). Details regarding correct responses are presented in Table B.3 in Appendix B. Patients and HC were comparable in terms of gender ratio ( $\chi^2 = 0.67$ ,  $p = .413$ ) but differed in age ( $U = 20$ ,  $p < .001$ ). Therefore, we performed a one-way rank analysis of covariance. A non-parametric version was performed since our data did not meet ANCOVA normality assumptions. When age was introduced as a covariate, the LTLE patients did not differ significantly from HC regarding correct responses ( $F(1,35) = 0.01$ ,  $p = .921$ ) and reaction time ( $F(1,35) = 3.16$ ,  $p = .084$ ).

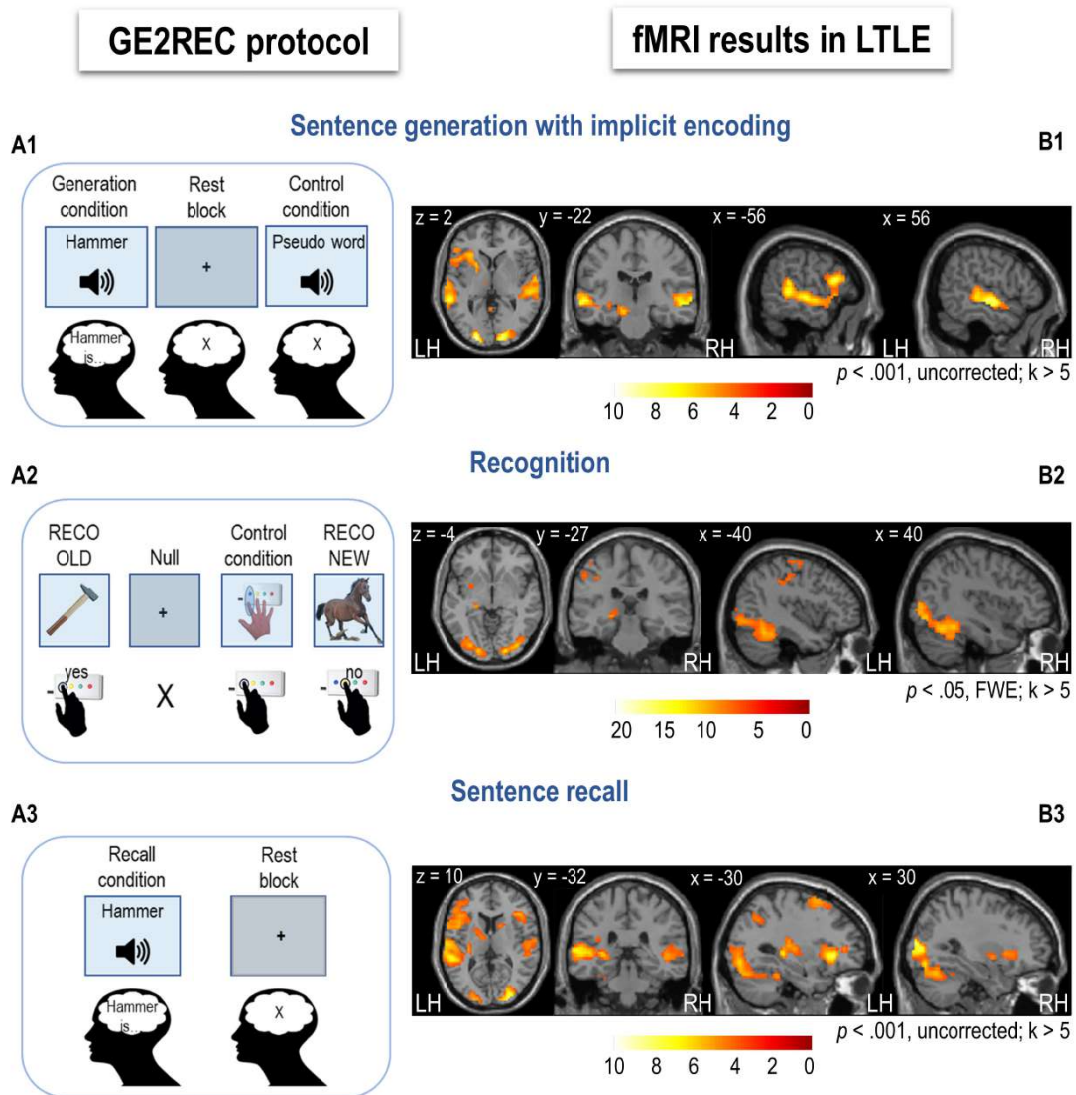
### 3.3.2 Functional MRI

Panel A of Figure 3.3 presents GE2REC tasks, and Panel B shows results obtained for the LTLE group.

**Sentence generation** activated a vast frontotemporal network, including bilateral temporal and predominantly left frontal regions (Figure 3.3, Subpanel B1 and Table B.4). The left inferior frontal, middle temporal, and bilateral superior temporal cortices were activated during this task. Bilateral but predominantly right cerebellar activation mainly of the lobule 6 and Crus 1 was obtained. Left hippocampal and parahippocampal activation was observed at a lower  $p$ -value ( $p < .001$ ). **Recognition** recruited a network that included the bilateral fusiform, occipital and inferior temporal, bilateral cingulum, and left superior frontal cortices, as well as left inferior parietal and left hippocampus (Figure 3.3, Subpanel B2 and Table B.5). Activation of the right hippocampus and inferior parietal lobule was also detected at a lower  $p$ -value ( $p < .001$ ). **Recall** activated a network that included bilateral superior frontal and left inferior frontal cortices, left middle and bilateral superior temporal cortices (Figure 3.3, Subpanel B3 and Table B.6). Bilateral occipital and left hippocampal activation was obtained at a lower  $p$ -value ( $p < .001$ ).

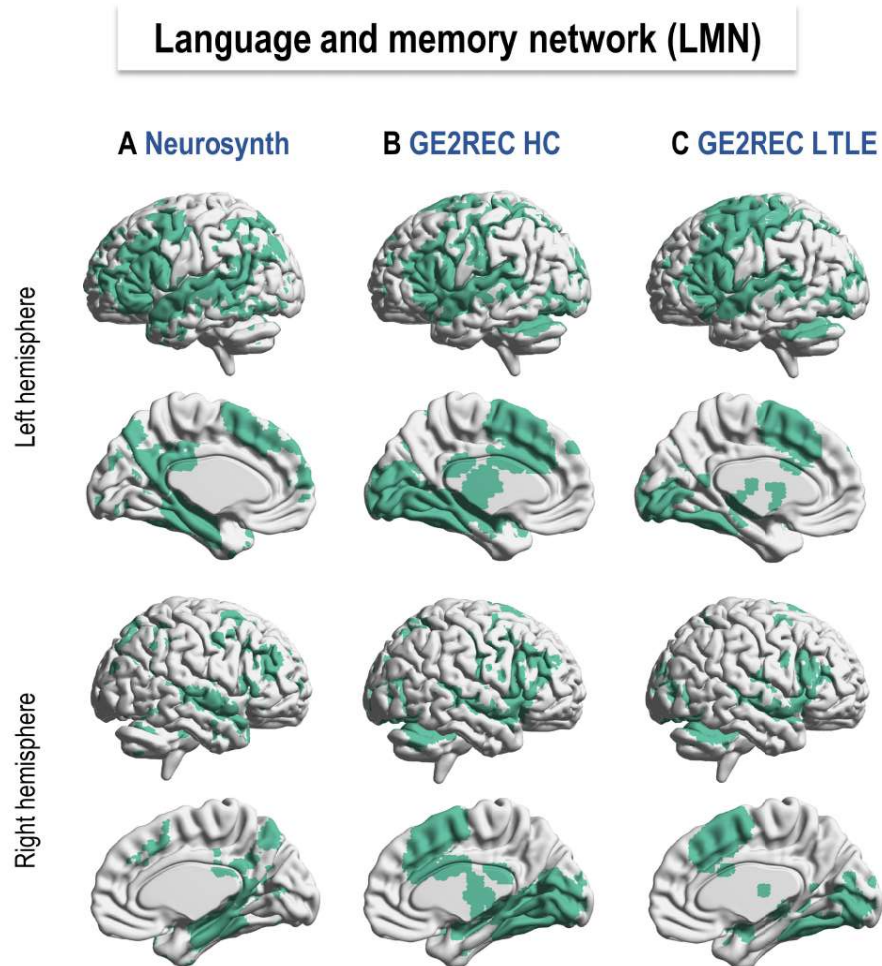
### 3.3.3 Correspondence between LMN networks

Figure 3.4 shows the LMN in HC and LTLE provided by Neurosynth meta-analysis (Subpanel A) and GE2REC protocol (Subpanels B and C; detailed results are presented in Table B.7). This comparison allowed us to claim that the LMN can be robustly activated using the three GE2REC runs. However, some differences with Neurosynth maps were noted in both HC and LTLE. GE2REC recruited less left prefrontal, left angular and parietal lobule than expected. On the other hand, GE2REC recruited more bilateral supplementary motor area (SMA), insula, occipital cortices, subcortical structures, and cerebellum in HC and LTLE (see Table B.7). Several regions were only common to GE2REC and Neurosynth in HC, such as the superior temporal pole, middle temporal gyrus, and bilateral hippocampi.



**Figure 3.3:** Schematic illustration of the GE2REC protocol (A) and activation maps (B) for each task in left temporal lobe epilepsy (LTLE) patients ( $N = 18$ ). (A1, B1) Sentence generation with implicit encoding with a block design. (A2, B2) Recognition task with event-related design. (A3, B3) Recall task with a block design. The activation maps are projected onto a 2D template using xjview toolbox <https://www.alivelearn.net/xjview>). The color scale indicates the T value. For illustration, LMN is presented at a more permissive threshold for sentence generation and recall ( $p < .001$ ,  $k > 5$ ). LH = left hemisphere; RH = right hemisphere.





**Figure 3.4:** Language and memory networks (LMN) resulting from Neurosynth database (A, Yarkoni et al., 2011), GE2REC in healthy participants (B), and LTLE patients (C). Specifically, a search for terms language and memory in the Neurosynth database yielded 1101 and 2744 studies, respectively. Maps were binarized and added up. GE2REC maps were based on activations provided by the second-level group analyses for HC (N=19) and LTLE (N=18) by all three tasks together. A less permissive threshold ( $p < .001$  and  $k > 5$ ) was used for binarization of GE2REC activation given the limited number of participants compared to the number of meta-analyses and participants in Neurosynth. The LMN correspondence between GE2REC and Neurosynth is reported in Table B.7 in terms of AAL regions (Tzourio-Mazoyer et al., 2002). LTLE = left temporal lobe epilepsy; HC = healthy controls.

### 3.3.4 LTLE vs. HC differences

Since LTLE and HC were comparable in terms of gender but not age, we controlled for the effect of age in all analyses. There were no regions more activated in LTLE than HC. Therefore, the results only indicate regions significantly more activated in HC than in LTLE. Specifically, sentence generation revealed more activation of bilateral inferior frontal opercular, parietal, and left superior temporal cortices in HC (Figure 3.5, Subpanel A1 and Table B.9). Recognition activated more the bilateral superior parietal, occipital, fusiform, and lingual gyri in HC (Figure 3.5, Subpanel B1 and Table B.10). Finally, we obtained more activation of right inferior pars opercularis and insula for recall in HC (Figure 3.5, Subpanel C1 and Table B.11).

### 3.3.5 Hemispheric lateralization and group differences

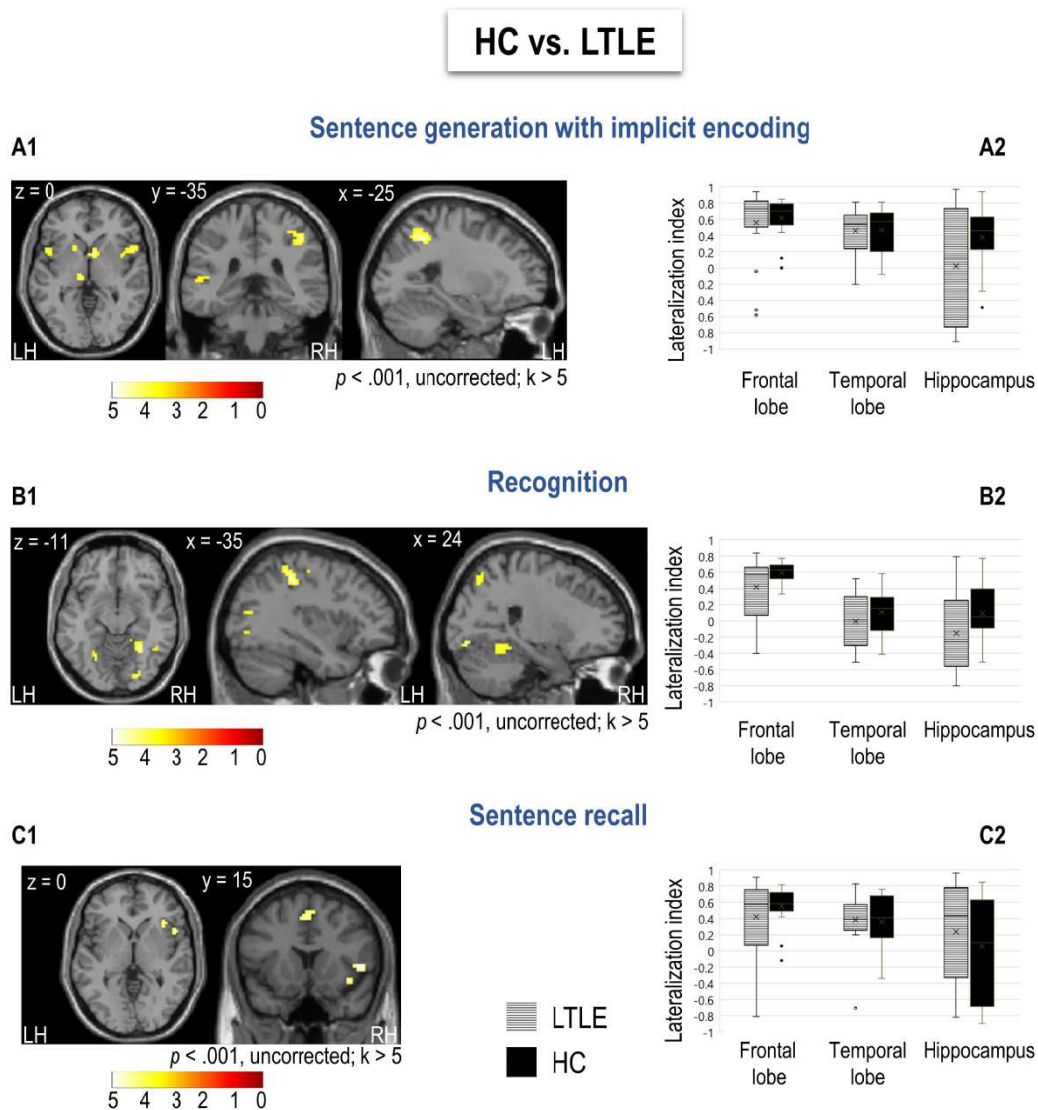
Figure 3.5 (Subpanels 2) and Table B.8 show lateralization indices for LTLE and HC for the three tasks. Man-Whitney U test showed that there were no group differences in frontal (GENE:  $U = 145$ ,  $p = .438$ , RECO:  $U = 138$ ,  $p = .323$ , RA:  $U = 167$ ,  $p = .903$ ) or temporal lateralization (GENE:  $U = 167$ ,  $p = .903$ , RECO:  $U = 135$ ,  $p = .274$ , RA:  $U = 163$ ,  $p = .808$ ). Regarding the hippocampal structure, the Man-Whitney U test did not show significant differences between the two groups (GENE:  $U = 124$ ,  $p = .158$ , RECO:  $U = 112$ ,  $p = .073$ , RA:  $U = 139$ ,  $p = .331$ ). However, when categorized based on their lateralization, LTLE patients show more frequently bilateral to right lateralization of the hippocampus during generation task than HC ( $\chi^2 = 4.68$ ,  $p = .031$ ). No such differences were found for the other tasks (RECO:  $\chi^2 = 3.34$ ,  $p = .068$ ; RA:  $\chi^2 = 0.67$ ,  $p = .413$ ). Interestingly, Levene's test showed that LTLE had variable LIs than HC for the hippocampus in the sentence generation task ( $F = 12.69$ ,  $p < .001$ ) and frontal lobe in the recognition ( $F = 16.45$ ,  $p < .001$ ) and recall tasks ( $F = 7.36$ ,  $p = .01$ ; see Table B.8).

Friedman test for repeated measurements showed a significant task effect on the temporal lobe's lateralization ( $\chi^2 = 12.4$ ,  $p = .002$ ), but not frontal in LTLE ( $\chi^2 = 1.44$ ,  $p = .486$ ). Specifically, the temporal lobe was less left-lateralized during the recognition task than during sentence generation ( $D = 4.01$ ,  $p < 0.001$ ) and recall tasks ( $D = 3.2$ ,  $p = 0.003$ ). This was comparable to HC, which also showed the task's effect in lateralization of the temporal ( $\chi^2 = 10.8$ ,  $p = .004$ ) but not the frontal lobe ( $\chi^2 = 4.11$ ,  $p = .128$ ). The temporal lobe was less left-lateralized during the recognition task than during the generation ( $D = 3.74$ ,  $p < .001$ ) and the recall task ( $D = 2.43$ ,  $p = .020$ ), similarly to LTLE.

The LTLE temporal lobe was generally less left-lateralized than the frontal lobe for the recognition task ( $\chi^2 = 5.56$ ,  $p = .018$ ) but not for the sentence generation ( $\chi^2 = 2$ ,  $p = .157$ ) and recall task ( $\chi^2 = 0.889$ ,  $p = .346$ ). However, in HC temporal lobe was less left-lateralized than the frontal lobe during all the tasks (GE:  $\chi^2 = 4.26$ ,  $p = .039$ , RECO:  $\chi^2 = 8$ ,  $p = .005$ , RA:  $\chi^2 = 6.37$ ,  $p = .012$ ).

### 3.3.6 Efficiency of language-and-memory (re)organization

We explored the cognitive efficiency of functional organization and reorganization by correlating lateralization of selected language and memory regions of interest (ROIs)



**Figure 3.5:** Differences between LTLE and HC for sentence generation, recognition, and recall. A1, B1, and C1 show functional maps for HC > LTLE obtained for each task (sentence generation, recognition and recall, respectively) at a threshold of  $p < .001$  and  $k > 5$ . Activations were projected onto 2D axial, coronal, and sagittal slices. The color scale indicates the T value. No significant difference was obtained for LTLE compared to HC. A2, B2, and C2 show distribution of lateralization indices calculated for frontal and temporal lobes and the hippocampus, resulting from each task in the group of LTLE and HC. The mean of each lateralization index distribution is indicated with an x sign and the median with a bar. LH = left hemisphere; RH = right hemisphere; LTLE = left temporal lobe epilepsy patients; HC = healthy controls.

with behavioral and cognitive scores. The following results survived corrections for multiple comparisons. In LTLE, AMI scores were negatively correlated with LI of inferior parietal region during sentence generation ( $r_s = -0.7$ ,  $p = .003$ ,  $p_{adj} = .018$ ), indicating that higher AMI scores were associated with higher right lateralization of this region. Semantic fluency scores were positively correlated with lateralization of the inferior frontal pars orbitalis ( $r_s = 0.65$ ,  $p = .005$ ,  $p_{adj} = .03$ ) for sentence generation, as an increase in semantic fluency scores was associated with higher left lateralization of this ROI. During recognition, lateralization of the inferior frontal pars triangularis ( $r_s = 0.61$ ,  $p = .009$ ,  $p_{adj} = .027$ ) and pars opercularis ( $r_s = 0.73$ ,  $p < .001$ ,  $p_{adj} = .001$ ) were positively correlated with phonological fluency scores, since higher scores were associated with higher left lateralization of these ROIs. There were no significant correlations between clinical variables and LIs after correction for multiple comparisons.

### Box 3.2 Summary of the main results

- Using the GE2REC protocol, we mapped the LMN network of LTLE patients;
- LTLE patients do not show one typical reorganization pattern on a group level but a widespread inter- and intra-hemispheric reorganization;
- LTLE patients show more bilateral-to-right hippocampal lateralization during sentence generation and encoding

## 3.4 Discussion

This chapter aimed to map LMN underlying the language and declarative memory interaction in a group of LTLE patients, candidates for surgery. To do so, we used the same protocol we previously used in the previous Chapter with healthy individuals. This protocol provides functional interactivity since each task demands both functions, and the three runs are interrelated. Specifically, during GE, participants perform word recognition, lexical-semantic search, and sentence production, as well as implicit encoding and contextual binding, particularly related to episodic memory (Yonelinas et al., 2019). RECO is based on object naming and memory recognition. Finally, RA engages word recognition, lexical-semantic search that triggers episodic retrieval and concept access, sentence recall, and sentence production. In terms of memory, this protocol assesses declarative memory since GE2REC task performance engages both episodic and semantic memory, also accessing different memory processes throughout the tasks (encoding – retrieval – recall).

The interaction between language and memory is essential for everyday functioning, and that calls for their joint investigation instead of trying to untangle them. This interaction is particularly significant in LTLE patients whose functions are often imperiled (Bartha-Doering & Trinka, 2014; Bell et al., 2011; Tramoni-Negre et al., 2017), more intertwined (Kellermann et al., 2016), and their (usually reorganized) representations are intermeshed (Tracy & Boswell, 2008). In addition to mapping the LMN

of LTLE patients, this study also aimed to investigate its reorganization compared to healthy individuals.

### 3.4.1 Did we manage to map LMN in LTLE?

As we saw in previous chapters reviewing studies, models, and meta-analyses (Benjamin et al., 2017; Labache et al., 2019; Price, 2012; Roger, Pichat, et al., 2020; Spaniol et al., 2009; Vigneau et al., 2006), the theoretical LMN network would engage an extensive bilateral but predominantly left-lateralized fronto-temporo-parietal network. It would include inferior frontal regions for lexico-semantic search and lexical production and bilateral mesial and lateral (middle and inferior) temporal and parietal cortices required for language, semantic and episodic memory processes. As illustrated in Figure 3.4, the GE2REC LMN corresponds to the LMN that emerges from the meta-analysis (see also Table B.7). However, some areas, such as prefrontal and parietal cortices, are not recruited by our protocol. The lack of parietal activation may be due to the fact that this protocol does not accentuate phonological processing (Cousin et al., 2007; Trébuchon et al., 2013). However, we showed engagement of some critical regions for language and memory, such as the putamen (Viñas-Guasch & Wu, 2017), the thalamus (Llano, 2016), and the cerebellum (see Addendum 1.1 in Chapter 1 Gatti et al., 2021; Keren-Happuch et al., 2014; Lœvenbruck et al., 2018), often “neglected” from the most important neurocognitive models of language and memory. Several temporal regions observed in HC were less recruited by LTLE, probably due to their pathology, especially the left temporal and hippocampi (Scharfman, 2015; Thom & Bertram, 2012).

### 3.4.2 How is LMN reorganized in TLE?

To understand how the integrative LMN is reorganized in LTLE, we will discuss differences between LTLE and HC based on all three GE2REC tasks and at a global instead of regional level within a meta-networking framework, as proposed by Herbet and Duffau (2020). LMN can indeed be considered as a meta-network as natural communication cannot operate based on one system without additional supporting systems (Hertrich et al., 2020).

Our LTLE patients showed widespread reorganization in the LMN, mainly manifested as lower activity of the regions having an integrative role or engaged in cognitive control (Binder & Desai, 2011; Burianová et al., 2017; Ranganath & Ritchey, 2012). Specifically, within the semantic network engaged by all three tasks, LTLE patients showed less activation of “convergence” regions (such as inferior parietal and fusiform gyri) and the regions involved with the control of goal-directed action and information selection (such as dorsomedial and inferior prefrontal cortices) (Binder & Desai, 2011; Forseth et al., 2018). Moreover, LTLE showed weaker activation of the inferior frontal gyrus (IFG), a region that integrates dorsal and ventral streams under the cognitive prefrontal control (Weiller et al., 2016).

Within memory networks, LTLE patients showed reduced activity of regions belonging to the posterior medial system that serves as an interface between semantic and episodic systems and as an integrator between modalities and subsystems (Palacio & Cardenas,

2019; Ranganath & Ritchey, 2012), such as precuneus (Binder & Desai, 2011), angular gyrus (Humphreys et al., 2021; Ranganath & Ritchey, 2012; Seghier, 2013), and thalamus (Wolff & Vann, 2019). As we saw in the introduction, the semantic-episodic distinction is softened since these two systems are interdependent and have overlapping neural correlates (see Chapter 1, section 1.3.1). Moreover, it was proposed that one of the underlying processes these systems share is cognitive control (Burianova et al., 2010; Vatansever et al., 2021). LTLE patients in this study indeed activated less the regions of ventral attention or salience network (SAL) and dorsal attention network (DAN, see Chapter 4 for more detail on large-scale networks). SAL is mainly engaged in coordinating attentional resources, cognitive control, and recruitment of resources for responding (Burianová et al., 2017; Hertrich et al., 2020). Within this network, LTLE showed decreased activation of the insula, anterior cingulate, and SMA. Concerning the DAN, involved in goal-directed and top-down attention (Dixon et al., 2017; Vossel et al., 2014), LTLE showed reduced activation of superior and inferior parietal, pre- and postcentral cortices. The disfunction of these networks, already identified in TLE (Burianová et al., 2017; Zhang, Lu, Zhong, Tan, Yang, et al., 2009), could result from long-term seizure propagation (Burianová et al., 2017). These effects might manifest as poorer coordination of attention and reduced allocation of attention to language and memory processes, leading to weaker activation of regions performing integration within semantic, syntactic, and memory subsystems and between them. Therefore, language and memory deficits observed in TLE (Dutta et al., 2018; Jaimes-Bautista et al., 2015; Tramoní-Negre et al., 2017) could be explained by the weaker cross-network interactions and dynamics due to poorer involvement of regions that act as an interface between multiple functional systems (Herbet & Duffau, 2020).

### 3.4.3 Hemispheric lateralization

In terms of hemispheric predominance in patients, although inter-hemispheric network reorganization is a common finding in LTLE (Baciu & Perrone-Bertolotti, 2015; Bonelli et al., 2012; Cousin et al., 2008; Foesleitner et al., 2021; Goldmann & Golby, 2005; Hamberger & Cole, 2011; Powell et al., 2007; M. K. Sidhu et al., 2013; Torlay et al., 2017), our patients did not show an evident inter-hemispheric reorganization as revealed by group-level analyses. This result can be explained by our patients' late age of seizures onset (ASO, see Table B.1), generally associated with intra-hemispheric reorganization, compared to patients with early ASO who more frequently show inter-hemispheric reorganization (Baciu & Perrone-Bertolotti, 2015). Additionally, patients were right-handed, less likely to show atypical lateralization (Mazoyer et al., 2014). However, the comparison of LIs calculated at a regional level showed that the lateralization of frontal and hippocampal regions was more variable in LTLE than in HC (Table B.8). This finding suggests that GE2REC manages to yield various types of LTLE-related reorganization, as showed by Berl et al. (2014), which, however, could not stand up as a unique pattern at a group level. Additionally, regional level analyses revealed that most patients did not show left hippocampal activation during encoding, suggesting reorganization at this level as reported by previous studies (Dupont & Vercueil, 2015; M. K. Sidhu et al., 2013).

We also note that regional lateralization tends to change across tasks in both HC and

LTLE. This finding is in line with previous findings suggesting that hemispheric lateralization for language is not a rigid and a unitary construct (Bradshaw, Thompson, et al., 2017; Bradshaw et al., 2019) but varies according to regions and specific processes. It was likewise found that different memory processes and types of stimuli could result in different memory lateralization (Andreau & Torres Batán, 2019; Golby et al., 2002; Milian et al., 2015; Palacio & Cardenas, 2019). One of the advantages of GE2REC is that it includes both verbal and visual material, different language and memory processes, allowing for a more complete preoperative screening of regional lateralization.

#### 3.4.4 How efficient is the reorganization?

Regarding cognitive efficiency in LTLE patients, we found that better semantic (verbal) and phonological fluency performance (Godefroy & GREFEX, 2008) was associated with greater left-lateralization of IFG (orbitalis and triangularis), one of the LMN integrative hubs (Banjac et al., 2021; Weiller et al., 2016). A previous study also found that verbal fluency scores correlate with left IFG activation in LTLE patients, suggesting its involvement in the functional integrity of language network in these patients (Bonelli et al., 2011). On the other hand, better memory performance (IMA, Wechsler, 2009) was associated with increased right-lateralization of the inferior parietal lobule. This region is a part of DAN and FPN control networks engaged in the attention and coordination of interaction between networks (Dixon et al., 2017; Vossel et al., 2014; Yeo et al., 2011). Indeed, attention difficulties can influence the auditory memory index (Holdnack & Drozdick, 2010). While the dorsal parts of attention networks usually show symmetrical engagement (Bartolomeo & Seidel Malkinson, 2019), the right lateralization of these regions was more beneficial for our patients. This finding could be interpreted as a compensatory mechanism of using additional executive resources from the right hemisphere, as observed in older adults (Baciu et al., 2021; Gertel et al., 2020). Taken together, our findings for cognitive efficiency suggest that LTLE have better cognitive performance if the LMN is relying more on the left hemisphere for integration processes and on the right hemisphere capacities for cognitive control.

#### 3.4.5 Study Limitations and perspectives

This study has similar limitations as the previous one (see section 2.4.5 in Chapter 2), such as response recording and the necessary level of language and memory conservation. In addition to that, using this protocol with patients revealed other limitations. For instance, the duration of tasks could have been longer to improve the signal-to-noise ratio, mainly for the medial temporal regions. However, a longer protocol was challenging to implement since the presurgical assessment already includes numerous examinations (MRI, MRI-DTI, PET, neuropsychological assessment). The total exam duration would thus be too long for patients. Nevertheless, to palliate this limitation, GE2REC recruits several memory types and processes, which increases the likelihood of medial temporal and hippocampal activation.

Also, due to the age difference between patients and healthy, we introduced age as one of the regressors. That could have affected the results. In future studies, it would be good if the control group was paired with patients. In this case and the study from

the previous Chapter, this was not possible. The main reason is that the protocol had to be validated on healthy subjects before being applied to patients. At the time of validation on healthy subjects, it was impossible to predict which patients would appear at the clinic and their age.

In addition, the results are certainly limited by the sample size. We will discuss this limitation in more detail, as this is one often cited in studies. As an illustration, if we were interested in detecting a phenomenon that is known to have a large-size effect ( $D = .8$ ) as a difference between two groups using a two-sample t-test (two-tailed), with 80% power and a threshold of  $\alpha = 0.001$  (usually used in fMRI studies), we would need 57 participants per group, or 114 participants in total (the calculation is made using the G\*power toolbox Faul et al., 2009). Some authors argue that a sample should have at least 16 (K. Friston, 2012) or 20 participants for a study to have sufficient reliability (Thirion et al., 2007). Other authors nevertheless argue for much larger sample sizes ( $>100$ ) (Turner et al., 2018). Pajula and Tohka (2016) concluded that inter-subject correlation results based on 20 participants converged close to the ones obtained with 130 participants. However, the split-half reliability of their results improved significantly when the sample was increased from 20 to 30 participants. Even though the statistical power in typically sized samples ( $n < 20$ ) is low (which is more than we had in our study), some authors argue that significantly active voxels tend to be true positives and that the number of false negatives is sizable (Garavan & Murphy, 2016). However, the authors also acknowledge specific reasons for smaller sample studies (Turner et al., 2018). For instance, although some power analyses tools for fMRI studies were proposed (e.g., Mumford, 2012), defining effect size in an fMRI context is not as conceptually apparent as in standard behavior studies (Turner et al., 2018). Indeed, the cost of fMRI studies is not negligible, and it cannot be overlooked in practice (Turner et al., 2018). Finally, the "time cost" is also essential and should be considered, especially when conducting a patient study. One cannot predict when a patient that fits all the study criteria will appear. Also, as evidenced in our data, even if diagnosed with the same disorder, patients have highly variable characteristics. Therefore, we can conclude that this study should be continued, and larger samples (both LTLE and HC) should be collected. Nevertheless, the existing samples allow us to at least form an idea and hypotheses about LMN and its reorganization in LTLE patients.

We have made hypotheses regarding the dynamics between the regions of LMN and various subnetworks that form it. However, functional connectivity analyses should be performed to evaluate the network properties of LMN and its dynamics. Moreover, for understanding the dynamics of LMN, it would be crucial to compare its resting-state functioning with the active state. We will address this in the next Chapter.

Finally, we stated that one of the benefits of using the language-and-memory perspective is to predict post-surgery outcomes. Based on the presented data, we are unable to make conclusions on that matter. The exact predictive power of examining interactive LMN for cognitive outcome in post-surgery should be determined in a larger cohort and associated with functional and structural connectivity data. We will address this in Chapter 5. Nevertheless, we have reasons to conclude that language-memory interaction can be explored in TLE patients using the proposed protocol.



### 3.4.6 Conclusion - the LMN that can be mapped in LTLE with GE2REC

The presented findings corroborate that interactive LMN can be examined using the proposed methodology. First, we found in LTLE and HC the LMN close to the expected one. Moreover, this protocol is sensible to different reorganization patterns (evidenced in higher lateralization variability in patients). Second, we found engagement of sub-cortical and cerebellar regions using this protocol, which can help understand LMN functioning. Third, using this method we provide a comprehensive assessment of patient's neurocognitive functioning since we assess in an intermeshed fashion, several language (mainly lexico-semantic and syntactic in comprehension and production) and memory (encoding, recognition and recall) processes, as well as the two types (semantic, episodic) of long-term memory, based on both visual and auditory modalities. The protocol design connects these processes horizontally (within-run) and vertically (between-runs). Forth, the medial temporal structures are variably activated, including the hippocampus, according to tested processes by each task. However, the activation of medial temporal structures is weaker than the activation of other regions. Given the difficulties of designing an fMRI protocol that activates these structures, this is a crucial aspect to be underlined (Buck & Sidhu, 2020; Haag & Bonelli, 2013; Powell & Duncan, 2005). To sum up, our group results showed that the LMN of LTLE patients is similar to that found in HC. Our patients did not show dramatic inter or intra-hemispheric LMN reorganization, but rather a mix of the two primarily manifested as lower activation of regions within the control networks and integrative LMN regions. These results suggest the importance of integration and coordination within multiple functional systems, such as the LMN.

Therefore, in the next chapter, we will investigate how are this integration and coordination achieved within LMN in healthy individuals and how it is reorganized in LTLE.

**Box 3.3 Main conclusions and open questions**

- Main conclusions
  - An extensive fronto-temporo-parietal network supports language-memory interaction in LTLE patients.
  - LMN of LTLE patients shows a combination of inter- and intra-hemispheric reorganization patterns described in the literature.
  - Left TLE patients show reduced activation of the regions involved in the integration of the LMN.
- Open questions
  - What is the functional dynamic of LMN in TLE?
  - How are the functional dynamics of LMN in TLE different compared to healthy individuals?
  - Can an individual patient's LMN enhance understanding of his/her cognitive difficulties?
  - What can the LMN and its reorganization of TLE patients tell us about their postoperative cognitive outcomes?

# Chapter 4

## LMN through the network prism

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This chapter is based on the paper [Banjac, S., Roger, E., Pichat, C., Cousin, E., Mosca, C., Lamalle, L., Krainik, A., Kahane, P., & Baciú, M. \(2021\)](#). Reconfiguration dynamics of a language-and-memory network in healthy participants and patients with temporal lobe epilepsy. *NeuroImage: Clinical*, 31, 102702.

## 4.1 Introduction/Context

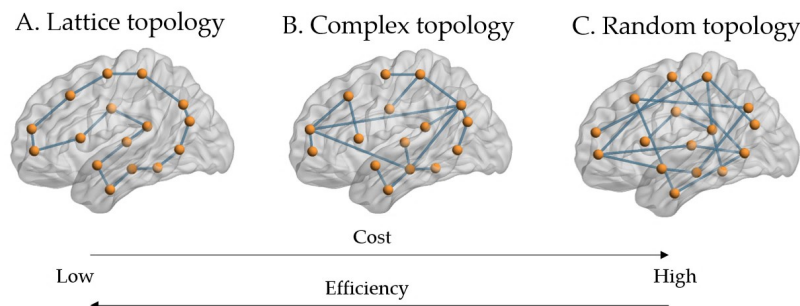
The previous chapters discussed the evidence supporting language-memory interaction, and we mapped this wide network in healthy individuals and LTLE patients. Throughout previous chapters, we have been referring to neural substrates in terms of networks. However, the standard fMRI task-based analyses do not reveal the communication between the regions within a network (Herbet & Duffau, 2020). Moreover, we stated that LMN is a meta-network composed of different subnetworks or parts of subnetworks. Therefore in this chapter we will explore the network properties and dynamics of LMN network(s).

### 4.1.1 The concept of networks

We are surrounded by and participate in various complex systems such as social networks, economies, or ecosystems. Development of methods for exploring those systems revealed that all these systems have some general properties of network organization. The field of network science emerged around the general analytic methods used to model complex networks (Fornito et al., 2016; Mitchell, 2009). One of such methods is Graph Theory, a mathematical field employed to model, estimate, and simulate the topology and dynamics of a network composed of interacting elements. A *graph* is used to model such networks. It is composed of *nodes* that are linked by *edges* (see Panel F of Figure 4.2). For instance, a node can represent a person, and the edge represents its social relationship with another person (node) (Fornito et al., 2016; Sporns, 2018). Graph theory quickly found its place within neuroscience that was in the transition from the localisationist perspective towards integrative and dynamic neurocognitive models (Dick et al., 2014; Farahani et al., 2019; Garcia-Ramos et al., 2016; Herbet & Duffau, 2020; Kellermann et al., 2016; Zamora-López et al., 2011, also see section 1.1). The nervous system can easily be modeled using a graph such as a neural connectivity matrix. In such a matrix, each row or column is a different brain region represented as a node in the graph (see Panel D of Figure 4.2). The value of each matrix element is represented as the edge. Matrix and graph are formally equivalent (Fornito et al., 2016).

The basic version of exploring human connectomics is to calculate the correlation between the time series of two anatomical locations. This statistical dependence between the time series of neuropsychological signals is called functional connectivity (FC). Hence, two areas are functionally connected if their dynamics show synchronization (Fornito et al., 2016). A (large-scale) functional network can, thus, be described as a collection of brain areas that interact to perform a specific function (Bressler & Menon, 2010).

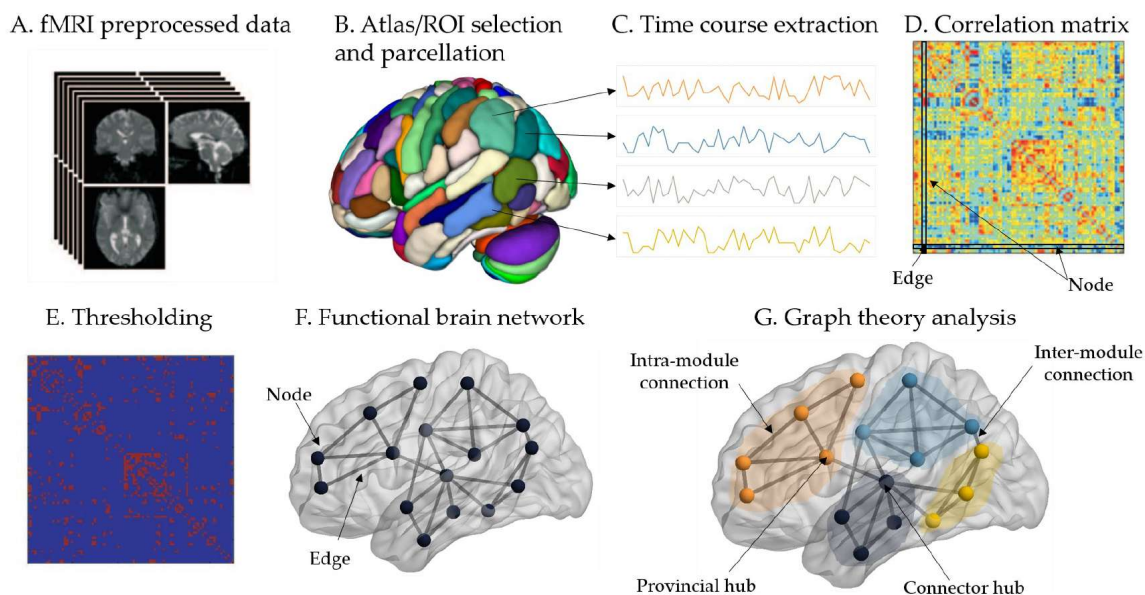
The functional organization of brain networks is governed by a drive to minimize material and metabolic costs while obtaining the most adaptive behavior (Achard & Bullmore, 2007; Bullmore & Sporns, 2012). Ramon y Cajal proposed that brain organization will be driven by lowering the axonal wiring cost (which conserves space) and reducing the conduction delay in the transmission of information between neurons (which conserves time) (Fornito et al., 2016). A lattice-like topology of a network minimizes the wiring cost (Panel A, Figure 4.1). Within this topology, each node has the same number of neighbors, making them identical statistically. However, this topology does not allow for efficient integration of information processing. On the other hand, a random topology maximizes brain efficiency for integrative processing (Panel C, Figure 4.1). However, the wiring cost of this topology is very high due to numerous long-distance connections. As anticipated by Ramon y Cajal, brain topology is between these two (Panel B, Figure 4.1 Achard & Bullmore, 2007; Bullmore & Sporns, 2012; Fornito et al., 2016). It contains clusters or groups of lattice-like short-distance connections, called modules that reduce the wiring cost. In addition, brain organization also has long-distance connections that are “expensive” but allow for the efficiency of information processing (Bullmore & Sporns, 2012). Hence, the brain network organization economy minimizes the wiring cost and maximizes the adaptive topological value (Bullmore & Sporns, 2012).



**Figure 4.1:** Examples of network topologies. (A) The lattice topology with low cost and low efficiency. Within this topology, each node has the same number of connections. (B) The complex topology minimizes the wiring cost and maximizes efficiency. It is the type of topology observed in the organization of brain networks. It contains clusters of highly interconnected nodes and also long-distance connections. (C) The random topology that has high efficiency but also high wiring cost due to its numerous long-distance connections. Figure adapted from Bullmore and Sporns (2012).

In terms of Graph theory, brain networks have a modular small-world architecture that allows segregated and integrated information processing (Achard & Bullmore, 2007; Bullmore & Sporns, 2012; Zamora-López et al., 2011). The small-world property refers to dense or clustered local connectivity with relatively few long-range connections. This topology can support segregated and distributed information processing, help resilience against pathological insults, and minimize wiring costs (Achard & Bullmore, 2007). Furthermore, the modular architecture also supports functional integration and specialization (Bertolero et al., 2015; Meunier et al., 2010; Park &

Friston, 2013; Sporns, 2013; Zamora-López et al., 2011). Modularity enables the adaptation of a global network to environmental changes (Finc et al., 2017; Meunier et al., 2010), shaping it into local modules or specialized communities composed of densely intra-connected regions (nodes) that share a specific function (segregation property). Modular networks also deal more efficiently with higher processing requests, and they show better resilience against insults (Bullmore & Sporns, 2012). These modules are sparsely connected with other communities via inter-module connections that provide the integration property (see Panel G, Figure 4.2 Guimerà & Amaral, 2005; Rubinov & Sporns, 2010; Sporns & Betzel, 2016).



**Figure 4.2:** The image shows the Schematic representation of graph theory analysis of brain networks. After preprocessing the fMRI data (A), ROIs are selected (B), and for each ROI, the time course is extracted (C). Each region’s time course is correlated with the other regions’ time courses. Based on this, a symmetric correlation matrix is constructed (D). Columns and rows within such a matrix represent ROIs (nodes), and the cells represent the correlation between them (edges). This correlation matrix is usually thresholded to remove weak correlations and to reduce the complexity (E). The functional brain network is constructed based on this matrix, with nodes representing the ROIs and edges representing their connections (F). Then the graph analysis is performed to obtain topological measures of the network (G). For instance, networks’ partition into communities, or modularity, can be explored. Densely connected subgroups of nodes are called modules or communities (orange, blue, dark blue, and yellow groups). Intra-module connections refer to links between the nodes of the same module, while inter-module connections are the links between nodes of different modules. Based on these connections, modules can have different roles. Provincial hubs are nodes that are highly interconnected within their communities but not with others. Connector hubs have numerous connections with the nodes within their and other communities. Figure adapted from Farahani et al. (2019) and Sporns and Betzel (2016).

Nodes can have different roles within this modular structure depending on their connections with other nodes within their module and those from other modules. Nodes that are highly interconnected within their communities but not so strongly to other communities are called provincial hubs, and they support segregation (Bertolero et

al., 2015; Meunier et al., 2010; Schedlbauer & Ekstrom, 2019). The integration between modules is based on the connector nodes that are highly connected with other communities and can be divided into satellites and connector hubs depending on their status within their community (Fornito et al., 2016; Guimerà & Amaral, 2005; Meunier et al., 2010). The difference is that connector hubs are, unlike satellites, also highly interconnected within their communities (Bertolero et al., 2015; Meunier et al., 2010; Schedlbauer & Ekstrom, 2019).

It is essential to remember that functional and structural connectivity (SC) concepts are not the same. While SC or anatomical connectivity is based on axons, dendrites, and gap junctions, FC refers to activity synchronization between brain areas (voxels, regions) during particular behaviors (Bressler & Menon, 2010; K. J. Friston, 2011). Therefore, SC changes slowly, while FC can change rapidly over time. Also, FC can imply SC, but not necessarily (Bressler & Menon, 2010; Fornito et al., 2016). In this work, we will be focusing on FC.

### 4.1.2 Is resting-state enough to understand a network's dynamics?

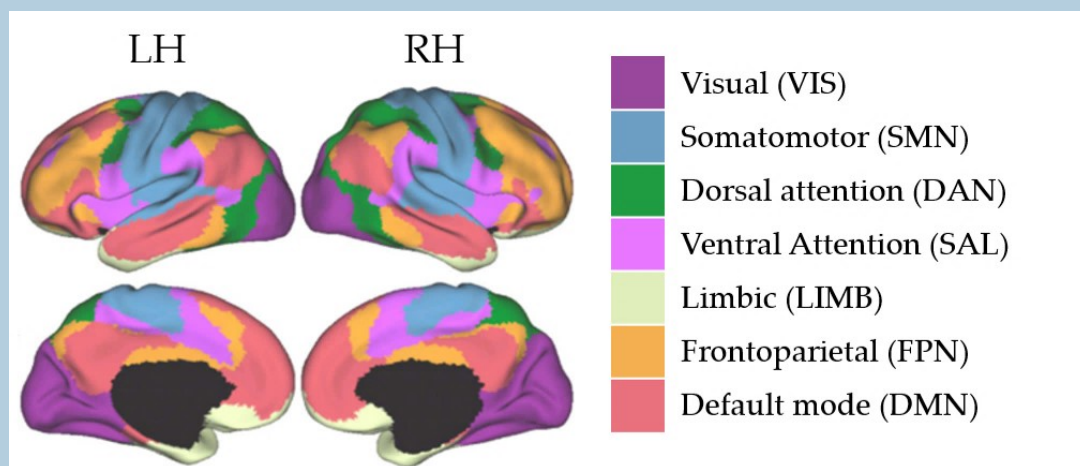
Traditionally, the FC was based on resting-state fMRI data (Farahani et al., 2019). This approach reveals large hierarchical and distributed brain networks related to various functional domains (see Addendum 4.1, Glasser et al., 2016; Power et al., 2011; Yeo et al., 2011), reflecting "intrinsic" activity intervening in the absence of any stimulation or task (Bolt et al., 2017; Bressler & Menon, 2010). Although these resting-state networks (RSN) are robust (De Luca et al., 2006; Yeo et al., 2011) and were found to be associated with behavior (e.g., Arnemann et al., 2015; van den Heuvel et al., 2009), it is difficult to make comprehensive conclusions on network architecture and connectivity, without considering the brain activity during a task (extrinsic brain activity). Moreover, when proposing that complex behavior is based on large-scale distributed networks, Mesulam (1998, 2000) suggested that cortical areas can dynamically shift affiliation from one network to another according to the task goal, following the principles of selectively distributed processing. These dynamic network reconfigurations support rapid associations and dissociations into functional subgroups that favor different network associations.

Studies exploring connectomic features of extrinsic or task-related networks have indeed found that they differ from intrinsic resting-state networks (Bolt et al., 2017; Cohen & D'Esposito, 2016; Mennes et al., 2013; Spadone et al., 2015) although others found significant similarities between them (Cole et al., 2014; Krienen et al., 2014). Therefore, intrinsic brain architecture does not provide a complete repertoire of extrinsic functional properties, such as flexible reconfiguration, when facing changing environment and task demands (Mennes et al., 2013). The differences between intrinsic and extrinsic networks were reported for the cognitive control (Mennes et al., 2013; Tomasi et al., 2014), working memory (Rzucidlo et al., 2013; Stanley et al., 2015), and semantic memory (DeSalvo et al., 2014).

### Addendum 4.1 Principal intrinsic networks

Various parcellations of the human cortex into intrinsic connectivity networks or resting-state networks (RSN) have been proposed. They usually consist of unimodal sensorimotor networks (e.g., motor, visual, auditory) and associative networks (e.g., default mode, frontoparietal, salience, and attention networks) (Uddin et al., 2019). Recent studies showed that the similarity between the sensorimotor networks across different atlases was high, while the higher-order networks had lower similarity (Doucet et al., 2019). There are also initiatives for establishing a universal taxonomy of functional networks (Uddin et al., 2019).

We present here the principal RSNs of interest for our work. This short overview should not be taken as an exhaustive list of all RSNs (for reviews, see Doucet et al., 2019; K. Smitha et al., 2017; Uddin et al., 2019). We mainly based on the parcellation proposed by Yeo et al. (2011).



The 7-network parcellation provided by Yeo et al. (2011).

**The frontoparietal network (FPN)** that mainly consists of the dlPFC and IPL is usually engaged in the demanding cognitive tasks for which rules must be retained. It is also sometimes termed executive network (K. Smitha et al., 2017). It engages in goal-directed guidance of behavior. Research has suggested that FPN regions engage in context-dependent regulation of thought and perception and therefore show significant flexibility (Dixon et al., 2017).

**Dorsal attention network (DAN)** engages in goal-directed executive control processes. DAN generally mediates attention in a top-down manner by guiding the voluntary allocation of attention to the task-relevant objects and when intrinsically relevant stimuli are identified (Dixon et al., 2017). DAN focuses on egocentric space (Koziol et al., 2016). However, it also has a close relationship with sensorimotor regions, plays a role in spatial perceptual attention, and shifts attention to salient objects (Dixon et al., 2017).

**The salience network (SAL)** includes the temporoparietal junction, SMA, the dorsal anterior cingulate cortex, the anterior part of the SMG, the frontal operculum, and the anterior insula (K. Smitha et al., 2017; Vessel et al., 2014; Yeo et al., 2011). It is also sometimes called the ventral attention network (Yeo et al., 2011). SAL is engaged in detecting unexpected stimuli and prompting attention shifts (Vessel et al., 2014). It is mainly focusing on the external world (Koziol et al., 2016). The malfunctioning of this network can disrupt the functioning of other networks since it manages the dynamic changes between them (K. Smitha et al., 2017).



**The limbic network (LIMB)** consists of anterior temporal lobes and the orbitofrontal cortex (Yeo et al., 2011). Regions of this network are sometimes considered part of the medial frontoparietal network (or the default mode network Uddin et al., 2019). The LIMB connects with the rest of the networks for motivational and reward influences.

**The default mode network (DMN)** consists of the anterior mPFC, posterior cingulate cortex, the posterior extent of IPL, the IFG, MTG, superior temporal sulcus, and parahippocampal cortex. Other regions that can constitute DMN but are less well characterized are the precuneus and retrosplenial cortex, the hippocampus, superior and middle frontal gyrus, and temporoparietal junction (Uddin et al., 2019). It was known as the task-negative network since it showed “deactivation” when a person engages in a task (K. Smitha et al., 2017). However, it was also linked with various cognitive functions, most frequently with different types of internally focused tasks such as autobiographical memory, imagining the future, and thinking about the perspective of others (Buckner et al., 2008). Additionally, it has been shown that semantic regions (such as AG, posterior cingulate cortex, and anterior temporal regions) that are part of DMN are the way through which factual knowledge is fed into our internal representations of past, present, and future episodes (Wirth et al., 2011).

Modern connectomic approaches (Cole et al., 2014; Fornito et al., 2016; Sporns & Betzel, 2016) allow to assess this state-dependent reconfiguration of brain architecture for specific cognitive functions and tasks (e.g., He et al., 2018; Hearne et al., 2017; Schedlbauer & Ekstrom, 2019) suggested by Mesulam (1998, 2000). Task-induced changes in network modularity can predict behavioral outcomes (Finc et al., 2017). Indeed, decreased modularity was observed for high cognitive demands (Finc et al., 2017; Hearne et al., 2017), and successful memory retrieval is associated with reconfiguration of modular structure (Schedlbauer & Ekstrom, 2019; Westphal et al., 2017). Overall, results suggest significant flexible reconfiguration of large-scale functional networks along rest and task-activity states for different cognitive functions (Bassett et al., 2011; Hearne et al., 2017; Yue et al., 2017).

However, most studies explored cognitive functions separately without investigating possible interactions between functions. To understand these interactions, it is essential to focus on the communication or the dynamics between the functions such as the language and declarative memory and its cerebral substrate, the language-and-memory network (LMN). Furthermore, a complete description of this language-memory interaction and underlying LMN should be based on extrinsic and intrinsic activities to capture the flexibility and dynamic architecture underlying its complex links.

### 4.1.3 What is happening with cerebral networks in TLE?

As stated in Chapter 1, a more comprehensive understanding of functional interaction based on the specific LMN network can be provided by studying conditions showing the reorganization of language and memory functions, such as TLE (Tracy & Boswell, 2008). As presented in Chapter 3, this neurological disorder is characterized by seizures induced by an epileptogenic network centered on medial temporal structures (Barr &

Morrison, 2015), associated or not with hippocampal atrophy (Thom & Bertram, 2012). The cognitive deficits of TLE patients suggest a dynamic relationship between language and declarative memory (Alessio et al., 2006; Allone et al., 2017; Bartha-Doering & Trinka, 2014; Tramoni-Negre et al., 2017; Zhao et al., 2014). Moreover, these patients show less clear segregation between cognitive domains (Kellermann et al., 2016). These findings also supports the necessity of evaluating language-memory interaction within a connectomic perspective instead each function separately (Waites et al., 2006). Findings presented in the previous chapter show that a significant reorganization of LMN occurs in TLE which could result from complex interactions between neurophysiological activity (epileptic activity) and neuroplasticity (Dinkelacker et al., 2016; Duffau, 2006).

Resting-state studies in TLE patients showed reduced functional connectivity (Betts et al., 2009) within "high-level" RSN such as DMN, DAN, SAL (Burianová et al., 2017; Liao et al., 2010; Zhang, Lu, Zhong, Tan, Yang, et al., 2009), as well as within "low-level" RSN such as auditory and sensorimotor networks (Zhang, Lu, Zhong, Tan, Liao, et al., 2009), and within language network (Waites et al., 2006). In addition, TLE patients showed reduced synchronization between multimodal "high-level" RSN (Burianová et al., 2017) and between "high-level" and "low-level" RSN (sensorimotor, Yang et al., 2018). Increased connectivity within medial temporal lobes together with decreased connectivity between them and distal networks (Englot et al., 2016; Haneef et al., 2014; Liao et al., 2010; Roger, Pichat, et al., 2020) were described in these patients and identified as dynamic diaschisis, a reorganization pattern based on hyper- and hypo-connected remotely-located regions (Cataldi et al., 2013; Roger, Pichat, et al., 2020). Liao et al. (2010) found that global topological measures of TLE functional networks are disrupted, showing reduced clustering using the resting-state data. Similarly, studies focusing on extrinsic activity found a global reduction in connectivity within language networks (Pravatà et al., 2011) and recruitment of additional networks located more posterior, due to anterior seizure activity (Protzner & McAndrews, 2011). Recently, He et al. (2018) reported that left temporal and right frontal regions in TLE patients showed reduced flexibility and ability to adapt to demands of a verb generation task dynamically. These regions also showed reduced communication with a core left frontal subnetwork. Overall, these authors suggested that the effect of pathology on network dynamics is more likely to manifest during language operations than during resting-state (He et al., 2018).

#### 4.1.4 The present study rationale

Given that most studies in healthy individuals and patients explored cerebral networks based on either intrinsic or extrinsic activity, it is difficult to understand how brain networks are dynamically reconfigured between resting-state and task-based activity. Additionally, as mentioned above, most studies did not directly address the interaction between language and declarative memory. Although we addressed this interaction in the studies presented in Chapters 2 and 3, they were based on classic task-based fMRI analysis, not allowing us thus to make conclusions regarding FC within LMN.

Therefore, this study is set to bridge this gap by evaluating both intrinsic and extrinsic LMN functional connectivity (FC) in healthy controls (HC) and TLE patients

and describe the network properties by using a graph theory approach (Fornito et al., 2016; Rubinov & Sporns, 2010). These analyses should help us understand the mechanisms supporting the language and declarative memory interaction based on LMN dynamic reconfiguration according to brain activity state (intrinsic, extrinsic) and physiological condition (health, epilepsy).

The intrinsic connectivity was assessed with a resting-state protocol, while the extrinsic task-based was evaluated with the GE2REC protocol presented in Chapter 2. We first explored segregation property by testing how LMN separates into modules for each state (LMN configuration) using a data-driven community detection algorithm (Blondel et al., 2008; Rubinov & Sporns, 2010; Schedlbauer & Ekstrom, 2019) and then analyzing the state reconfiguration (i.e., how the configuration changes between intrinsic and extrinsic state) in healthy participants. Then we explored the integration of LMN modules based on connector hubs first within each configuration and then comparing them to evaluate state reconfiguration. The reorganization of LMN configurations and state reconfiguration in terms of segregation and integration was tested using the same approach in TLE patients and comparing the results between the groups. We evaluated the cognitive efficiency of reorganization in TLE patients by associating cognitive scores with several parameters of segregation and integration.

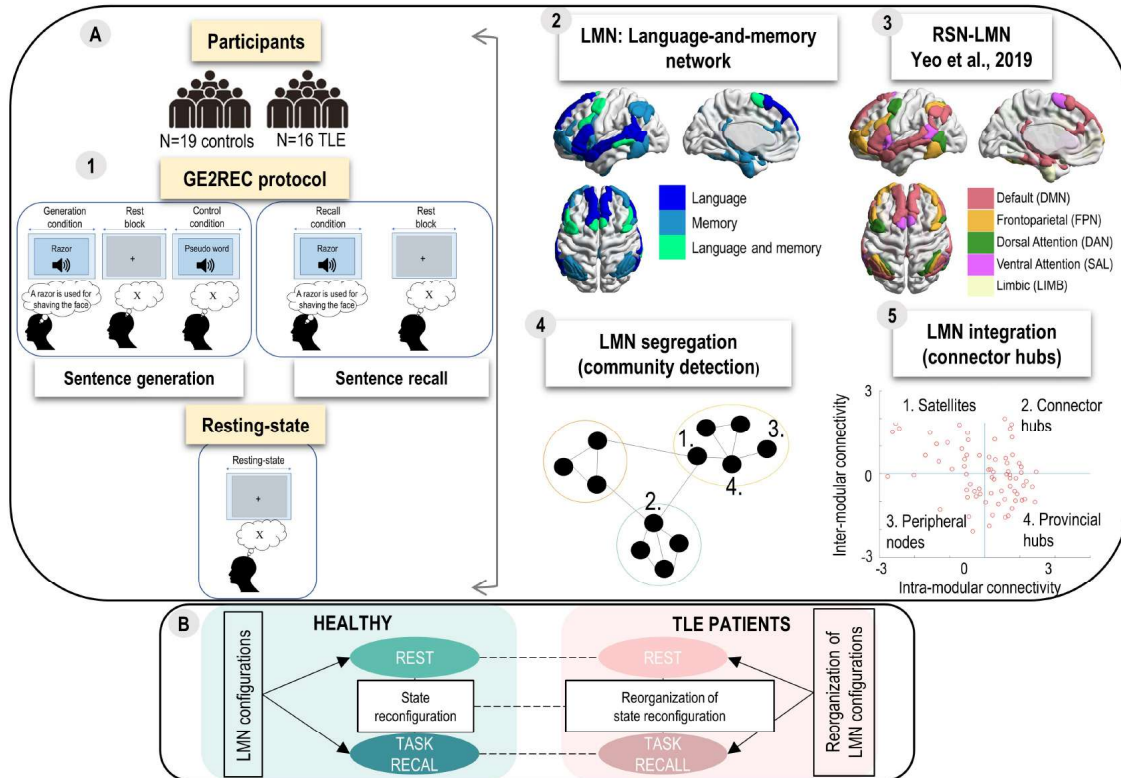
Based on the previous research, we expected that modular brain structure in HC shows less segregation during the task due to a more complex cerebral activity required by the task. In addition, regions exhibiting more flexibility between states should be the ones that allow for functional integration. Furthermore, TLE patients should show alterations of the modular structure due to disruption of functional connectivity and reduced flexibility of temporal regions. The potential difference between HC and TLE in "connector" regions should reflect compensatory mechanisms used by patients.

#### Box 4.1 Why should LMN be studied through the network prism?

- Complex systems, such as the brain, demonstrate network organization.
- Brain networks have a modular small-world architecture that allows segregated and integrated information processing.
- Engagement in a task (extrinsic state) is followed by changes in network modularity (such as decrease of modularity or reconfiguration of modules) compared to resting-state (intrinsic state).
- TLE patients show changes in FC within RSN and between them both during the intrinsic and extrinsic states.
- LMN dynamic reconfiguration between the intrinsic and extrinsic state in healthy individuals should indicate the mechanisms supporting the language and declarative memory interaction.
- The potential reorganization of LMN reconfiguration in TLE patients should reveal the compensatory mechanisms language-memory interaction relies on when a part of the LMN network is imperiled.

## 4.2 Material and Methods

A schematic illustration of the study design is presented in Figure 4.3.



**Figure 4.3:** Schematic representation of study pipeline. (A) Schematic representation of methodology. (A1) The healthy participants ( $N = 19$ ) and TLE patients ( $N = 16$ ) performed resting-state and the sentence recall task. (A2) We focused on the LMN ROIs defined in previous work (Roger, Pichat, et al., 2020). (A3) ROIs were separated based on the resting-state network (RSN) they belonged to. (A4) We performed community detection in two groups and two tasks to explore LMN configurations, state reconfiguration, and reorganization. (A5) We determined the role (connector hub, provincial hub, satellite, or peripheral node) of each LMN region based on its connectivity within a module (intra-modular connectivity) and with other modules (inter-modular connectivity). To explore LMN integration and its state reconfiguration, we focused on the connector hubs. The roles are schematically presented on Subpanel A4 with numbers corresponding to the role in Subpanel A5. (B) Schematic representation of main terms and analyses. Both segregation and integration of LMN were explored for each state, extrinsic and intrinsic (state LMN configuration), and its reconfiguration between the states in healthy participants (green). LMN configurations and state reconfiguration in terms of segregation and integration were tested using the same approach in TLE patients (pink), and the differences in LMN configurations and state reconfiguration between healthy controls and TLE patients (dashed lines).

### 4.2.1 Participants

Nineteen healthy volunteers (age  $21.2 \pm 2.97$ ; 9 females; all self-reported right-handed) and 16 TLE patients (11 left TLE and five right TLE, age  $33.8 \pm 10.5$ ; 9 females; 14 right-handed) were included in the study. The handedness was determined according to The Edinburgh Handedness Inventory (Oldfield, 1971). The demographic

and clinical features are presented in Tables C.1 and C.2. Participants were native French speakers and had a normal or corrected-to-normal vision. Patients were diagnosed with drug-resistant temporal epilepsy between 2017 and 2019. Neurologists made the diagnoses based on the recommendations of the ILAE committee report (Fisher, Acevedo, et al., 2014; Scheffer et al., 2017; Wieser et al., 2001) and a synthesis of several evaluations (clinical, scalp/depth-EEG, MRI/PETscan). Patients were candidates for curative surgery, and the fMRI evaluations were performed as a part of their presurgical assessment.

### 4.2.2 Neuropsychological data in patients

All patients underwent complete neuropsychological assessment, including language and memory functions carried out by a neuropsychologist and a speech therapist. This general cognitive assessment was used to analyze further the efficiency of LMN configurations and state reconfiguration in TLE patients. Specifically, the following cognitive scores were used in the analyses: (a) language scores: verbal comprehension index (VCI; WAIS-IV, Wechsler, 2008), naming (DO80, Deloche & Hannequin, 1997), semantic fluency (SFL), and phonological fluency (PFL Godefroy & GREFEX, 2008); and (b) memory scores: auditory memory index (AMI), immediate memory index (IMI) and delayed memory index (DMI; WMS IV, Wechsler, 2009). Test scores were standardized by gender, age, and sociocultural level. Detailed data on patients' cognitive performance is presented in Table C.3.

### 4.2.3 Experimental protocol

Participants first performed the GE2REC protocol presented in the previous chapters. This study focused on the sentence recall task (abbreviated RA) to access brain networks that reflect the language and declarative memory interaction. We decided to focus on this task for two reasons. First, because, among GE2REC tasks, it is the closest to everyday experiences. Second, in this task, participants were explicitly asked to rely on both language and memory.

Following the recall run, each participant underwent a resting-state for 13.20 min to measure intrinsic cerebral activity. Participants were required to lay down into the magnet and rest with eyes open while fixating a cross centered on the screen during the entire acquisition period.

### 4.2.4 MR acquisition

The MR acquisition procedure for the RA task and the anatomical volumes was the same as described in Chapters 2 and 3. During resting-state, four hundred cerebral rs-fMRI volumes were acquired using a gradient echo-planar imaging sequence (FEEPI, 36 axial slices, 3.5 mm thickness, TR = 2.0 s, TE = 30 ms, flip angle = 75°, the field of view = 192 x 192 mm, in-plane voxel size = 3x3 mm).

## 4.2.5 Prior data analysis and data preprocessing

### Statistical analyses of demographic, clinical, and neuropsychological characteristics

We included TLE patients with the left (LTLE) and right (RTLE) origin of seizures. Previous studies showed that LTLE and RTLE patients could differ regarding cognitive functioning and neural organization (de Campos et al., 2016; Phuong et al., 2020; Roger, Torlay, et al., 2020). Therefore, before conducting the primary analyses planned in this study, we tested whether our sample's LTLE and RTLE patients significantly differed regarding their clinical characteristics (age, epilepsy duration, number of AEDs<sup>1</sup>, hippocampal atrophy and gender), hippocampal volume, and neuropsychological performance. We did not flip the images of patients in the L-R direction in line with recommendations (Lee et al., 2018) since previous research found significant asymmetries in functional connectivity between two hemispheres mirrored over the longitudinal fissure (Raemaekers et al., 2018). Previous studies showed that epilepsy patients more often show atypical language lateralization than healthy participants (Baciu & Perrone-Bertolotti, 2015; Berl et al., 2014). A recent study also showed that language lateralization is related to functional connectivity of the language system and the whole-brain organization (Wang et al., 2019). Due to this, we controlled language lateralization by only including participants with left lateralization of language activation in the frontal lobe and left to bilateral activation in the temporal lobe. That way, we wanted to exclude the possibility that the potential differences of LMN community structure between healthy participants and TLE patients result from differences in language lateralization. The lateralization indices (LI) were calculated on frontal activations during the GE task using the bootstrap method of the SPM LI toolbox (Wilke & Lidzba, 2007, see also the section B.1 in the Appendix B). The differences between LTLE and RTLE patient groups on mentioned characteristics were tested using the Mann-Whitney U and Chi-square tests.

### Functional MRI preprocessing

The preprocessing was performed as described in Chapter 3.

### Network analysis

**Language-and-memory network: Parcellation and node definition.** ROIs of LMN explored in this study were previously defined in the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA, Joliot et al., 2015) and validated by (Roger, Pichat, et al., 2020). Despite standard left lateralization of language network, we tested the nodes across both hemispheres since language reorganization in TLE patients can be interhemispheric (Baciu & Perrone-Bertolotti, 2015; Balter et al., 2019) and given that language engages non-dominant hemisphere in healthy subjects (Hickok & Poeppel, 2007; Vigneau et al., 2011). Additionally, we have separated the hippocampus into anterior and posterior parts since various reorganization patterns were found for the anterior and posterior hippocampal networks (Li et al., 2017).

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<sup>1</sup>AED = Antiepileptic Drugs.

We also used specific ROIs for anterior and posterior hippocampi (left and right) for each participant, given that in patients, the hippocampal atrophy may have significant effects (Roger, Pichat, et al., 2020). However, subject-specific hippocampal ROIs for healthy participants were also used to avoid any artificial differences between two groups of participants. Subject-specific hippocampal ROIs were generated from T1w anatomical images with the Vol-Brain processing pipeline (Manjón & Coupé, 2016, available at <http://volbrain.upv.es>). This pipeline provided subject-specific MNI-registered hippocampal ROIs. These subject-specific hippocampal ROIs' anterior and posterior parts were defined by overlapping with anterior and posterior hippocampal masks of the AICHA atlas (Joliot et al., 2015). The final LMN network comprised 74 ROIs (37 per hemisphere). Subpanel A2 of Figure 4.3 shows the LMN on a brain template, and a list of ROIs is provided in Table C.5.

ROIs were also classified according to their membership to a specific resting-state network. For this purpose, we used the seven resting-state networks (RSN) atlas defined by Yeo et al. (2011). To precisely determine which RSN network each LMN region belonged to, the LMN was overlaid with the RSN map (Yeo et al., 2011). The number of overlapping voxels with each network was calculated for each region. An ROI was determined to belong to the RSN with which it had the largest percentage of overlapping voxels. Subpanel A3 of Figure 4.3 shows LMN ROIs according to their RSN.

**Connectivity analyses.** The FC within the LMN was calculated based on the resting-state and the recall activity using a Graph theory (GT) analysis (Fornito et al., 2016; Rubinov & Sporns, 2010). The CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2017, available at [www.nitrc.org/projects/conn](http://www.nitrc.org/projects/conn)) (Functional Connectivity Toolbox, Gabrieli Lab, Massachusetts Institute of Technology) was used to obtain FC matrices, and the Brain Connectivity Toolbox (BCT, Rubinov & Sporns, 2010, available at [sites.google.com/site/bctnet](http://sites.google.com/site/bctnet)) and GraphVar toolbox (Kruschwitz et al., 2015, available at [www.nitrc.org/projects/graphvar](http://www.nitrc.org/projects/graphvar)) were used for graph theory analyses. The CONN Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2017) provides ROI-to-ROI correlation analysis according to the temporal fluctuations of BOLD signals. The first step consisted of denoising the preprocessed unsmoothed data by regressing out the BOLD signal from the white matter, the CSF, outliers, and movements obtained by ART and SPM. For the recall task, we also entered a separate regressor for the experimental condition in the regression, according to other previous studies validating this approach (Cao et al., 2014; Cole et al., 2014; Mohr et al., 2016). The resulting residual time series were temporally filtered to remove low-frequency scanner drifts and/or high-frequency physiological noise using band-pass filtered (0.008-0.09 Hz) for the resting-state and high-pass filter (0.008 Hz) for the recall task. Resting-state data processed in this way reflected intrinsic network, while those resulting from the recall task reflected extrinsic network. Then the Z score of the r-Pearson correlation coefficient was calculated for each participant by CONN toolbox for every possible pair of residual time series (2701 pairs of 74 ROIs of the LMN). In agreement with previous studies (Bolt et al., 2017; Cohen & D'Esposito, 2016), especially the one using a similar community detection algorithm (Schedlbauer & Ekstrom, 2019), the negative correlations were set to zero. However, the algorithm was also run with preserved negative correlations for validation purposes, and the main findings remained similar (see Figure

C.1). The resultant 74x74 matrices were then used in the statistical analyses described after this.

## 4.2.6 Data analysis

### LMN segregation

**LMN configurations and state reconfiguration.** Modularity or community detection enables a data-driven network partition into modules showing segregation properties (Fornito et al., 2012; Sporns, 2013). A community detection algorithm was performed in healthy participants to analyze LMN state configurations. Data-driven community structure was assessed by applying a modularity maximization algorithm (Louvain greedy algorithm, Blondel et al., 2008; Rubinov & Sporns, 2010) to individual correlation matrices with positive, weighted edges for each state separately. Given that the community partition can vary with each run of the algorithm (Rubinov & Sporns, 2010), we applied a consensus approach (Lancichinetti & Fortunato, 2012; Sporns & Betzel, 2016) similarly to prior studies (Dwyer et al., 2014; Hearne et al., 2017; Schedlbauer & Ekstrom, 2019). The applied approach estimated the most stable network partitions within a group across algorithm iterations and the thresholds proposed by Schedlbauer and Ekstrom (2019). A detailed explanation of the procedure is provided in section C.1.1 of Appendix C. The community detection on group level provided the modular partition, or LMN configuration, for each state and its corresponding modularity index  $Q$  showing the degree to which the matrix could be subdivided into non-overlapping modules (Rubinov & Sporns, 2010, 2011). The modules of the final network partitions were named based on the neuroanatomical localization of regions that were forming them. To test state reconfiguration in terms of segregation, we calculated the difference in the optimal group modular decomposition measured via the modularity index  $Q$  between states and the variation of information (VIn) to explore if the module partitions differ between the states. VIn quantifies the information intrinsic to the two partitions corrected by the information they share (Meilă, 2007). To test the statistical significance of index  $Q$  difference and VIn, we implemented a repeated measure permutation procedure (Dwyer et al., 2014; Hearne et al., 2017) explained in detail in section C.1.3 of Appendix C. Using the group modular partitions, we identified the regions that altered their module alliance between the states, called "movers" (Schedlbauer & Ekstrom, 2019). The reconfiguration of modules was quantified by a proportion of reconfiguration (pr) obtained by dividing the number of regions within a resting-state module that change the module during the task with the number of regions within that resting-state module.

**Reorganization of LMN configurations and state reconfiguration.** To test the reorganization of LMN configurations, we performed the above-mentioned data-driven community detection algorithm in TLE patients. We calculated the change of modularity index  $Q$  and VIn to explore the reorganization of state reconfiguration. Additionally, the community detection was performed individually for TLE patients providing the modular partition and modularity index  $Q$  for each state and participant (see section C.1.2 in Appendix C). Based on this, the state reconfiguration on the individual level was calculated as the difference between modularity index  $Q$  for two states



and between the number of modules. These TLE individual-level analyses aimed to test the effectiveness of LMN configurations and state reconfiguration by relating them to clinical and neuropsychological characteristics of patients.

We tested the significance of the difference between LMN configurations and state reconfiguration observed in healthy participants and the reorganization observed in TLE patients in three ways. First, we tested the significance of the difference between groups in segregation and modular partition of LMN configurations during each state using mentioned repeated measure permutation procedure for the difference of group-level modularity index  $Q$  and  $V_{in}$  of group partitions. Second, we analyzed physical distances within and between observed modules to test the group differences in how modules were segregated in LMN configurations. The euclidian distance was calculated between the regions that composed one module and between regions forming different modules (Alexander-Bloch et al., 2013). We compared mean within modules and between modules distances among groups for each state using the two-sample  $t$ -test. Third, since our patients' epileptogenic zone is situated in the temporal lobe, we tested if TLE patients differed from healthy participants in terms of the ability of these regions to change modules during state reconfiguration. This was done by comparing the number of "movers" in the temporal and frontal lobe between the groups using the Chi-square test.

## LMN integration

**LMN configurations and state reconfiguration.** To analyze the integration in the observed LMN community structures, we calculated the roles of the regions within each LMN configuration in healthy participants. Topological roles were assigned to each node based on its intra- and inter- modular connections. To that end, we calculated normalized intra-modular degree ( $z$ , Meunier et al., 2009), whose value is higher if a node has a large number of intra-modular connections compared to other nodes in the same module. We measured inter-modular connectivity with the participation coefficient ( $P_c$ , Rubinov & Sporns, 2010). Due to the narrow distribution (Schedlbauer & Ekstrom, 2019) and dependency on the number of modules (Fornito et al., 2016), the  $P_c$  value was standardized within a given community partition ( $P_{cs}$ ). As in previous studies, the intra- and inter-modular planes were divided into four domains due to the smaller number of nodes within LMN (Meunier et al., 2009; Schedlbauer & Ekstrom, 2019). Nodes were considered as connector hubs if they had both high  $z$  ( $\geq 0$ ) and  $P_{cs}$  ( $\geq 0$ ) and as provincial hubs, if they had high intra-modular connectivity ( $z \geq 0$ ) but low  $P_{cs}$  ( $< 0$ ). Nodes that had low  $z$  ( $< 0$ ) were considered as satellite nodes if they had high  $P_{cs}$  ( $\geq 0$ ), or as peripheral nodes, if their  $P_{cs}$  was low ( $< 0$ ) (Guimerà & Amaral, 2005; Meunier et al., 2009; Schedlbauer & Ekstrom, 2019). The roles were determined based on each state's final group modular partition and the corresponding across-subjects mean FC matrices for group-level roles or corresponding individual FC matrices for individual-level roles. Nodes and their respective roles were grouped based on the RSN network nodes belonged to. State reconfiguration in terms of integration was tested by analyzing the number of connector hubs between two states in healthy participants using the Mann-Whitney for each network using the individual-level data (i.e., number of connector hubs in each participant). We also analyzed the

role distribution of each group's "mover" regions using the Chi-square Goodness of Fit Test.

**Reorganization of LMN configurations and state reconfiguration.** The same analysis was performed in TLE patients to test the reorganization of LMN configurations and state reconfiguration. Moreover, to test the difference between LMN state reconfiguration and its reorganization in terms of integration, we compared the change in the number of connector hubs within each RSN network between the groups. To this end, the change in the number of connector hubs was calculated as the difference between the number of connector hubs during the rest and during the recall task for each network and participant. Finally, the Mann–Whitney U test was used to test the differences in the connector hub change between the healthy participants and TLE patients for each network separately. The results were FDR corrected for multiple comparisons.

To analyze in more detail the possible disorganization of LMN integration in patients, we calculated a specific graph theory parameter, the hub disruption index (HDI, for more information on the calculation of this index, see Achard et al., 2012; Roger, Pichat, et al., 2020) with Pcs values for LMN configurations. The HDI can indicate whether the integration property of a specific region or node is increased or decreased. The HDI was first calculated on a group level to compare groups and check if there is a general reorganization or disruption of inter-modular integration in TLE patients. The groups were compared with a two-sample t-test. Additionally, we calculated the HDI on the regional level to identify regions that show the highest increase/decrease of inter-modular connectivity between the groups.

**The efficiency of the reorganization of LMN configurations and state reconfiguration.** The efficiency of the reorganization of LMN configurations and state reconfiguration observed in TLE patients was tested in two ways. First, the Spearman correlation was calculated between standardized language and memory scores (Table C.3) and a) individual modularity index Q and the number of modules for each state and their change between states and b) HDI values. Second, TLE patients were divided into a high or low-performance group for each neuropsychological test, depending on whether their score was above or below the group median. Then the Mann-Whitney U test was used to analyze the differences between high and low performers on FC parameters. For these analyses, both uncorrected and FDR corrected values are reported. The results that do not pass FDR correction are regarded as only exploratory.

## 4.3 Results

### 4.3.1 Statistical analyses of demographic, clinical, and neuropsychological characteristics

We first tested the similarity between left and right TLE patients before combining them in one group. There were no significant differences in demographic and clinical data and neuropsychological scores between left and right TLE subgroups (Table C.3).

There was no intra-group difference between left and right hippocampi in neither of the patient groups (LTLE:  $U = 39$ ,  $p = .158$ ; RTLE:  $U = 16$ ,  $p = .465$ ). When compared to healthy participants, the LTLE patients had smaller left hippocampus ( $U = 52$ ,  $p = .024$ ), while the volume of the right hippocampus volume was not different ( $U = 86.5$ ,  $p = .438$ ). No significant differences were found between the RTLE patients and healthy participants with respect to the volume of hippocampi (left:  $U = 41$ ,  $p = .644$ ; right:  $U = 23$ ,  $p = .082$ ). Activations during the language task were found to be consistently left-lateralized ( $LI > 0.2$ ) in the frontal lobe for all TLE patients ( $U = 39.5$ ,  $p = .173$ ) and they did not differ from healthy participants ( $U = 196.5$ ,  $p = .140$ , Table C.6 provides LIs of all participants). In addition, temporal lobe language activations were mostly left-lateralized and there was no difference between TLE patients ( $U = 21.5$ ,  $p = .496$ ) or between patients and healthy ( $U = 158.5$ ,  $p = .829$ ).

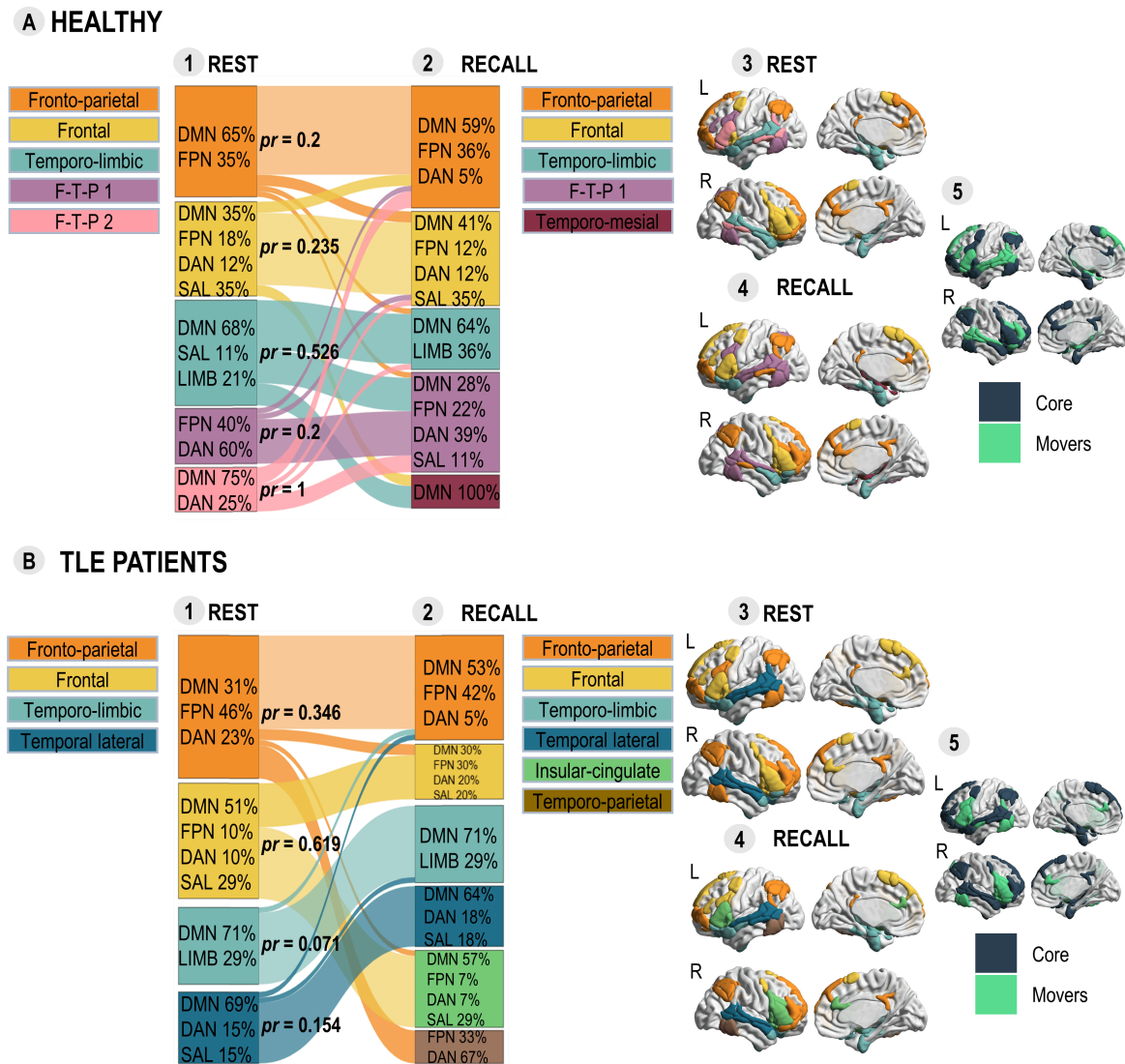
Since no significant differences between left and right TLE patients were found, we finally combined them and analyzed them as a single patient group. Nevertheless, the descriptive statistics of the main network parameters for LTLE and RTLE are presented in Table C.14.

### 4.3.2 LMN segregation

#### LMN configurations and state reconfiguration

Based on a data-driven community detection algorithm, we identified state configurations that show how LMN splits into separate modules (i.e., a subset of highly interconnected regions) during each state (Bullmore & Sporns, 2012; Fornito et al., 2016; Meunier et al., 2010). Our results showed that healthy participants' resting-state and task LMN configurations were composed of the same number of modules with no significant difference between the modularity indexes  $Q$  ( $\Delta Q = 0.02$ ,  $p = .391$ ). Although the number of modules was the same, their composition (i.e., partition) was different between the states ( $V_{In} = 0.34$ ,  $p < .001$ ). Module partitions and reconfigurations of resting-state modules in healthy participants are shown in Panel A of Figure 4.4, and module affiliation of each region is provided in Table C.5.

The proportion of reconfiguration ( $pr$ ) used to quantify the extent to which the resting-state modules changed compared to the task is presented in Subpanel A1 of Figure 4.4, and Table C.5 provides details on the movement of each region. The most reconfigured modules in healthy participants were the second DMN-DAN fronto-temporo-parietal ( $pr = 1$ ) and the temporal-limbic module ( $pr = .526$ ).



**Figure 4.4:** Segregation of LMN in community structures found in healthy participants (A) and TLE patients (B) during the two states. The alluvial diagrams present the dynamics of state reconfiguration of modules from resting-state (1) to sentence recall (2) in healthy participants (A) and its reorganization in TLE patients (B). For each module, the composition is indicated in percentages of networks that form a given module. For each resting-state module, the proportion of reconfiguration ( $pr$ ) is indicated. The architectures of modules are presented in the templates (3 and 4). A5 and B5 show the “core” regions of healthy participants and TLE patients that remain in the same module from rest to task (dark blue) and “movers” that change their module (light green). F-T-P = Fronto-temporo-parietal module, REST = resting-state, RECALL = sentence recall task.

### Reorganization of LMN configurations and state reconfiguration

In TLE patients, the transition between the states was accompanied by a change of the number of modules, as indicated by a significant difference between the modularity indexes  $Q$  ( $\Delta Q = 0.05$ ,  $p < .05$ ), and the module partitions were significantly different between the two states ( $VIn = 0.22$ ,  $p < .001$ ). The extrinsic configuration of LMN in TLE patients was found to be more modular and comprised of a higher number

of modules than healthy participants ( $\Delta Q = 0.07$ ,  $p < 0.01$ ). At the same time, the difference was not significant between intrinsic configurations ( $\Delta Q = 0.004$ ,  $p = 0.727$ ). In addition, both resting-state ( $V_{In} = 0.31$ ,  $p < .001$ ) and task ( $V_{In} = 0.33$ ,  $p < .001$ ) modular partitions were significantly different between two groups. Module partitions and reconfigurations of resting-state modules in TLE patients are shown in Panel B of Figure 4.4, and module affiliation of each region is presented in Table C.5.

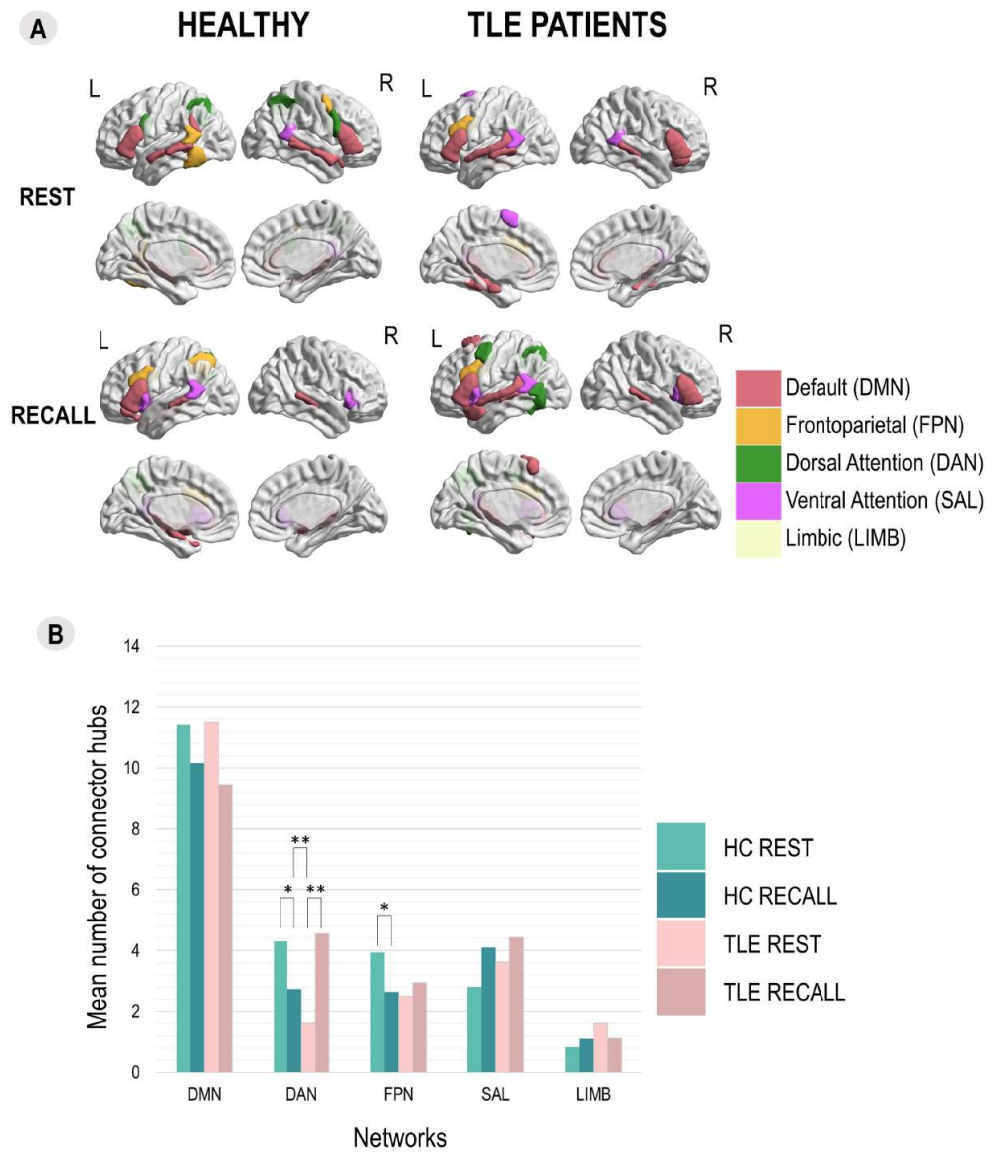
Additionally, our results indicated that the anatomical (i.e., Euclidean) distance of the regions within modules was significantly smaller in TLE patients than in healthy participants during the task ( $t = 2.562$ ,  $p < 0.05$ ). In other words, regions within modules of TLE patients were anatomically closer to each other than in controls. Furthermore, the temporo-limbic ( $pr = .071$ ) and temporal lateral module ( $pr = .154$ ) in TLE patients showed the smallest change. Consistent with this result, a Chi-square test showed that that mesial and lateral temporal regions were less flexible (i.e. having less "movers") in TLE patients compared to healthy participants ( $\chi^2(1, N=56) = 7.29$ ,  $p < .01$ ), while the flexibility of frontal regions was not different between the groups ( $\chi^2(1, N=48) = 0.1$ ,  $p = .755$ ).

### 4.3.3 LMN integration

#### LMN configurations and state reconfiguration

The integration properties were explored via connector hubs, especially their reconfiguration between the tasks. Panel A of Figure 4.5 shows the regions that were connector hubs in more than 50% of participants of both groups across the states. Table C.7 presents the roles of LMN regions based on their normalized intra-modular degree and standardized participation coefficient obtained with the across-subjects mean FC matrices. Our analyses showed that in healthy participants (Figure 4.5, Panel B), fewer regions belonging to DAN ( $U = 78.5$ ,  $p_{FDR} < 0.05$ ) and FPN ( $U = 99.5$ ,  $p_{FDR} < 0.05$ ) were connector hubs during recall compared to the rest.

Additionally, to explore the regions that changed modules between the states (i.e., "movers"), we analyzed the distribution of their roles across states. Our analyses showed that "movers" were more often connector hubs and satellite nodes during both states in healthy participants (REST:  $\chi^2(3, N=532) = 116.72$ ,  $p_{FDR} < .05$ ; RA:  $\chi^2(3, N=532) = 125.79$ ,  $p_{FDR} < .05$ ) having thus primarily the connecting roles. Table C.8 provides the role distribution of "movers" across states and groups.



**Figure 4.5:** The integration of LMN was assessed via the distribution of connector hubs between groups and tasks. (A) Topography of the most common connector hubs according to groups and tasks. We present the regions that were connector hubs in more than half of the group (10/19 in healthy and 9/16 in TLE patients). The colors of the regions represent their network affiliation. (B) Distribution of connector hubs according to groups and tasks for each network showing LMN state reconfiguration and LMN reorganization in terms of integration. Significant differences at the  $p < 0.01$  threshold with FDR correction are marked with \*\* and those at  $p < 0.05$  are marked with \*. HC = healthy controls, REST = resting-state, RECALL = sentence recall task.

### Reorganization of LMN configurations and state reconfiguration

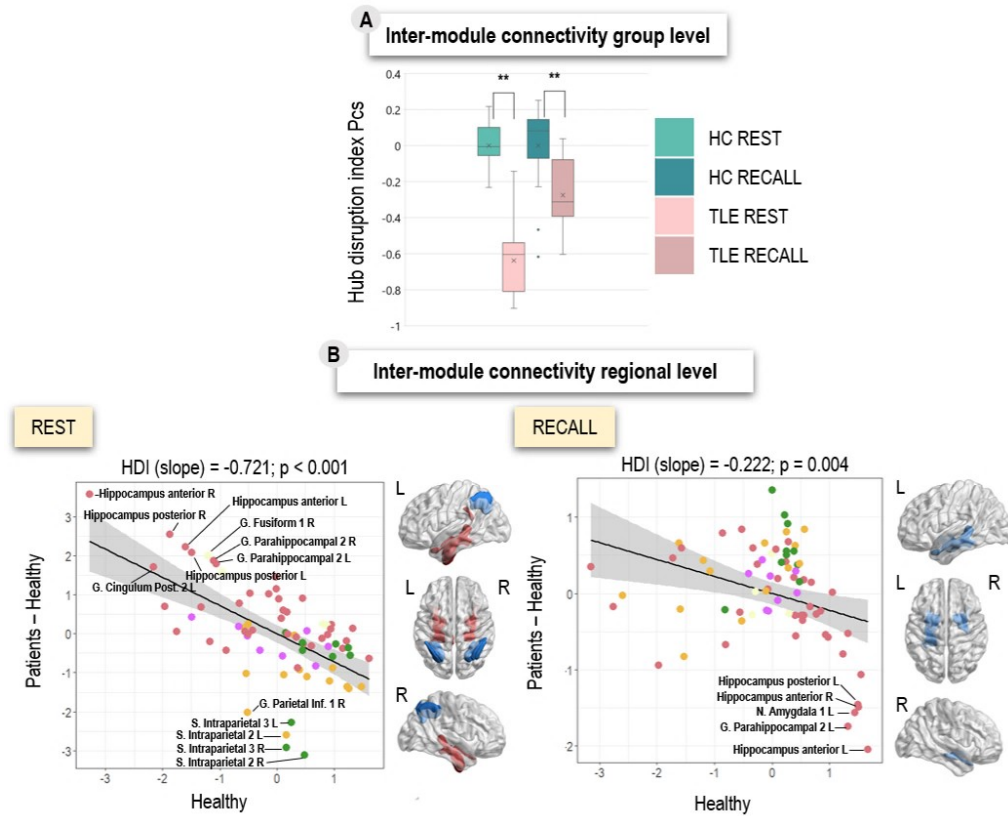
In TLE patients, higher number of DAN regions were connector hubs during recall than during the rest ( $U = 227.5$ ,  $p_{FDR} < 0.01$ ). Interestingly this variation was different between groups for DAN ( $U = 16.5$ ,  $p_{FDR} < 0.01$ ). Detailed results are presented in Tables C.9 and C.10. Moreover, the "movers" in TLE patients were also more often connector hubs and satellite nodes during both states (REST:  $\chi^2(3, N=400) = 14.12$ ,  $p_{FDR} < .05$ ; RA:  $\chi^2(3, N=400) = 147.02$ ,  $p_{FDR} = .543$ ).

Our HDI results (Figure 4.6) indicated that TLE patients showed significant disruption of inter-modular connectivity in both states compared to healthy participants (REST:  $t = -11.65$ ,  $p_{FDR} < 0.01$ ; RA:  $t = -3.86$ ,  $p_{FDR} < 0.01$ ). We further explored this inter-modular connectivity disruption on a regional level. The biggest disruption of inter-modular connectivity in patients during resting-state was found within FPN and DAN (bilateral intraparietal sulci). At the same time, the increase was observed within DMN (bilateral hippocampal gyri, right fusiform, bilateral parahippocampus, and left posterior cingulate gyrus). Conversely, the biggest disruption of inter-modular connectivity during the task in patients was identified within DMN (bilateral anterior hippocampus, left posterior hippocampus, bilateral amygdala, and left parahippocampus).

#### 4.3.4 The efficiency of the reorganization of LMN configurations and state reconfiguration

The efficiency of the reorganization of LMN configurations and state reconfiguration found in TLE patients was tested using the Spearman rank correlation and the Mann-Whitney U test. The obtained results were not significant after FDR correction. The results are presented in Tables C.11 and C.12.

Since there was a significant age difference between healthy participants and TLE patients ( $U = 269$ ,  $p < .001$ ), we tested if the principal network parameters are age-related and the potential effect of age. There was no significant effect. Detailed results are presented in Table C.13.



**Figure 4.6:** Reorganization of LMN state configurations in terms of integration (inter-modular connectivity) expressed via HDI (hub disruption index). (A) Group differences between healthy participants and TLE patients regarding HDI for resting-state and sentence recall. Differences that are significant after the FDR correction on the  $p < 0.01$  level are marked with \*\*. (B) The differences in inter-modular connectivity on the regional level between two groups for each state. The colors of the regions represent their network affiliation. Template representations show regions with the greatest differences between the groups. Blue regions show the greatest decrease in inter-modular connectivity in patients compared to control, and regions in red show the greatest increase. HC = healthy controls, REST = resting-state, RECALL = sentence recall task, HDI = hub disruption index.



**Box 4.2 Summary of the main results**

- The intrinsic-extrinsic LMN reconfiguration in HC is manifested through the change of module composition and the same level of segregation, while there is a higher segregation in TLE.
- Regions within extrinsic modules of TLE patients were anatomically closer to each other than in HC.
- During the task that demanded language-memory interaction, there is a segregation of the temporo-mesial (hippocampo-amygdalar) module in HC, which is not the case in TLE patients.
- TLE patients had significant disruption of inter-modular integration in both states compared to healthy individuals.
- During intrinsic-extrinsic LMN reconfiguration, HC showed a reduction of connector hubs that belonged to DAN, while TLE showed an increase.

## 4.4 Discussion

In the present study, we were interested in the dynamics between regions and networks within LMN that is a cerebral representation of the language-memory interaction. We hypothesized that the LMN configuration is dynamic so that it reconfigures according to brain activity (intrinsic, resting-state; extrinsic, task-induced) and condition (normal, HC; neurological, TLE patients). LMN configurations, state reconfiguration dynamics, and their reorganization were assessed by measuring the segregation (community detection) and the integration (connector hubs and inter-modular connectivity) properties. Our objective was to determine how LMN reconfigures across states (resting vs. task-induced) and groups (healthy vs. TLE patients) to support language-memory interaction.

### 4.4.1 LMN dynamics in healthy individuals

Analyses were first performed for HC to assess LMN configurations and state reconfiguration. Contrary to our expectations, the segregation did not vary across intrinsic and extrinsic states regarding the number of modules. However, rest and task differed in modular compositions of LMN configurations in line with the idea that task-related reconfigurations are necessary as an adaptation to task demands (Cohen & D'Esposito, 2016). More specifically, the LMN-intrinsic configuration included the following five modules (see Figure 4.4, Subpanel A1): fronto-parietal, frontal, temporo-limbic, and two fronto-temporo-parietal. The second fronto-temporo-parietal module includes language key regions (left triangularis and orbitalis, left superior and middle temporal, SMG), which agrees with previous results revealing correlated activity of language systems during rest (Alavash et al., 2019; Muller & Meyer, 2014). The segregation of LMN extrinsic configuration, illustrated in Figure 4.4 (Subpanel A2), shows five modules: fronto-parietal, frontal, temporo-limbic, fronto-temporo-parietal, and temporo-mesial.

There were two main segregation changes in task compared to rest in HC: (a) language key–regions from second fronto-temporo-parietal module migrated to other modules; (b) the hippocampus and amygdalae of temporo-limbic module migrated into a separate temporo-mesial module (Figure 4.4, Panel A). The temporo-mesial module in the sentence recall task could be engaged in the episodic retrieval and simultaneous encoding processes, as well as in the binding of retrieved episodes and lexico-semantic information into a coherent experience (Cooper & Ritchey, 2020; Ranganath & Ritchey, 2012). Therefore, the temporo-mesial (hippocampo-amygdalar) module and its dynamics across states may serve as a specialized interface between language and memory, as Duff and Brown-Schmidt (2012) suggested. This module that emerges during the task could be supporting language and declarative memory based on its flexible interactions with various cortical networks enabling both episodic retrieval (Geib et al., 2017; Westphal et al., 2017) and language processing (Covington & Duff, 2016; Piai et al., 2016). The composition of the first fronto-temporo-parietal module changed in task compared to rest by including supplementary lateral temporal regions required by lexico-semantic and syntactic processes typically recruited during a sentence recall task (Matchin & Hickok, 2020; Menenti et al., 2012). In conclusion, regions showing modular shifts between states in HC (see Figure 4.4, Subpanel A5) were those regions described as essential either for language (Hertrich et al., 2020; Middlebrooks et al., 2017; Price, 2012) or for memory (Ranganath & Ritchey, 2012; Reagh & Ranganath, 2018).

State reconfiguration of modular composition in HC concerned mainly regions with satellite or connector hub role (see Table C.8), as previously suggested (Schedlbauer & Ekstrom, 2019). Additionally, the majority of "movers" that had a connecting role (either as connector hub or satellite node) belonged to DMN such as the middle and posterior temporal, superior frontal, and prefrontal regions that were proposed to connect DMN to other networks, especially language network, providing thus DMN with linguistic information (Gordon et al., 2020). Globally, the segregation and integration results suggest that LMN state reconfigurations described in HC are mainly based on the modular flexibility of connector nodes when facing task requirements.

#### 4.4.2 LMN dynamics in TLE patients

The further objective of this study was to understand LMN configurations and state reconfigurations in patients with TLE. The state reconfiguration of LMN showed an increase in segregation and significant changes in modular composition. LMN was composed of four modules in its intrinsic configuration during rest: fronto-parietal, frontal, temporo-limbic, and temporal lateral (Figure 4.4, Subpanel B1) and six in its extrinsic configuration (Figure 4.4, Subpanel B2) during the task: fronto-parietal, frontal, temporo-limbic, temporal lateral, insulo-cingulate and temporo-parietal. Compared to HC, TLE did not show specific modules composed of language key regions (second fronto-temporo-parietal in HC) during rest. Also, lateral superior and middle temporal regions merged into one specific temporal lateral module during rest and task, which was not the case for HC. Additionally, the temporo-limbic module composed of memory key regions was smaller and limited to anterolateral temporal regions in patients compared to HC during rest. The mesial temporal module did not separate from the

temporo-limbic module during the task. Correspondingly, temporo-limbic and lateral temporal modules showed reduced flexibility during state reconfiguration of LMN, as did temporal regions in general compared to HC (Figure 4.4, Panel B). The location of the epileptogenic zones can explain the reduced reconfiguration ability of these modules and regions in patients in temporal regions (Barr & Morrison, 2015; Thom & Bertram, 2012), so the epileptic discharges could be preventing normal reconfigurations of these regions.

The compensatory mechanism for the absence of the language-memory interface, represented as hippocampo-amygdalar module in HC, was, therefore, the joining of the hippocampus to the temporo-limbic module together with the regions of the AM system (inferior frontal orbitalis, Ranganath & Ritchey, 2012) and semantic network in general (fusiform gyrus and lateral anterior temporal region, Binder & Desai, 2011). Notably, this module did not show substantial changes during state reconfiguration. The coupling of the hippocampus with the elements of the semantic system is in line with the semantic-episodic continuum (Irish & Vatansever, 2020; Renoult et al., 2019). Other elements of the declarative system help the malfunctioning hippocampus in its usual functions, which additionally burdens the temporo-limbic extrinsic module already engaged in semantic processing. This finding and interpretation could explain the difficulties in episodic retrieval and naming that are regularly observed in TLE patients (Allone et al., 2017; Bartha-Doering & Trinkka, 2014; Tramoni-Negre et al., 2017). Furthermore, this is consistent with the finding that reduced ability to retrieve episodic information is followed by more semantic details (Seixas-Lima et al., 2020), and that in general, if the hippocampus fails to complete a pattern during episodic retrieval, semantic information will be generated (Reagh & Ranganath, 2018).

Furthermore, the segregation of insulo-cingulate module in TLE during the task can be related to the task demands for overt speech inhibition (Løevenbruck et al., 2018; Oh et al., 2014). Similarly, the temporo-parietal module composed exclusively of DAN and FPN regions in TLE patients during the task can be explained by an additional requirement of control processes during the task (Dixon et al., 2017). The segregation of insulo-cingulate and temporo-parietal modules can indicate a compensatory mechanism, suggesting that compared to HC, TLE patients need more effort to control covert speech and more cognitive control to perform the combined language-and-memory task. Notably, regions were grouped into modules more based on their physical proximity in TLE patients. This is contrary to what could be expected for complex cognitive tasks such as the recall task, which generally rely on long-range integrative connections (Cohen & D'Esposito, 2016). This finding can be explained by the loss of distant connections in TLE as a result of epileptic discharges and their high metabolic cost, as previously suggested (Cohen & D'Esposito, 2016; Englot et al., 2016; Haneef et al., 2014; Lee et al., 2018; Liao et al., 2010; Roger, Pichat, et al., 2020). The local organization of modules and their greater segregation may benefit patients since it can prevent dysfunction or damage propagation throughout the network (Fornito et al., 2016).

LMN integration and its change between states were assessed via connector hubs in HC and TLE patients, and the two groups were compared. Patients showed an increased number of DAN connector hubs during task compared to rest (Figure 4.5, Panel B), suggesting that patients rely more on DAN regions for enabling the communication

and the cooperation between language and memory processes and networks due to dysfunctions within DMN which generally assures this interface (Bettus et al., 2009; Duff & Brown-Schmidt, 2012; Waites et al., 2006). TLE patients indeed have difficulties in language and memory tasks performance (Allone et al., 2017; Bell et al., 2011; Tramoni-Negre et al., 2017), which is probably the reason they need additional resources that DAN provides.

### 4.4.3 Disruption of inter-modular integration in TLE

Additional HDI analyses revealed that TLE patients show disruption of inter-modular integration (Figure 4.6, Panel A). The regional HDI analyses demonstrated that DMN shows a decrease. In contrast, DAN and FPN show an increase of inter-modular connectivity in task compared to rest in TLE patients relative to HC. Hence, TLE patients may rely less on DMN and more on DAN and FPN to flexibly increase their integration between states flexibly. In addition, we also found the "hippocampal paradox" (Figure 4.6, Panel B) previously described in TLE (Roger, Pichat, et al., 2020). Namely, even though global DMN connectivity is reduced in TLE, nodes, such as the hippocampus, can show hyper-connectivity (Cataldi et al., 2013). We found increased inter-modular connectivity of mesial temporal structures only during rest in line with other studies (Haneef et al., 2014; Roger, Pichat, et al., 2020). According to Englot et al. (2016), the increase in connectivity of these regions may be explained by the epileptic activity without any compensatory role. This explanation is supported by the decrease of inter-modular connectivity of these regions during the task (Figure 4.6, Panel B). Our results on LMN integration in TLE altogether suggest that classical language-memory interactions typically based on DMN regions as an interface (especially mesial temporal structures, Duff & Brown-Schmidt, 2012) may be disabled in TLE patients, which is compensated by control networks, in particular, the DAN and FPN. The integrative dysfunction of DMN in TLE is due to the loss of long-range connections (Lee et al., 2018).

### 4.4.4 Limitations and perspectives

Our study has several limitations. First of all, the study's low statistical power made it difficult to detect correlations with neuropsychological performances. The efficiency of reorganization should be explored in larger samples (see section 3.4.5 of Chapter 3 for the discussion on sample size). Also, a larger sample of TLE patients might allow separating left and right TLE patients and examining the effects of epileptogenic zone lateralization on modularity. Second, although we aimed to describe the dynamics of reconfiguration, our results are limited by the temporal resolution of the fMRI technique. Future studies could deepen our findings and hypotheses of language and declarative memory model using dynamic functional connectivity or a combination of fMRI with electrophysiological data. Furthermore, functional connectivity is based on correlation, so we can only discuss association without concluding causality. Therefore dynamic causal modeling could be beneficial for exploring the direction of the interaction between DAN and FPN with DMN. Like previous studies (Bolt et al., 2017; Cohen

& D’Esposito, 2016; Schedlbauer & Ekstrom, 2019; Stanley et al., 2015), we based our analyses only on positive connections, and we implemented an algorithm aiming to get the most stable network partitions across algorithm iterations and thresholds. Nevertheless, since there is no consensus on graph theory decisions, the presented findings and conclusions may not necessarily generalize to other studies using different network parameters. Moreover, the order of task and resting-state could have influenced the results (Tailby et al., 2015). Unfortunately, we were unable to change this aspect of our experimental procedure due to clinical practice. Future studies should examine the stability of modular structure with respect to the order of tasks. Finally, the ROIs of the LMN used in these analyzes were obtained from the meta-analyzes (Labache et al., 2019; Roger, Pichat, et al., 2020; Spaniol et al., 2009). Although LMNs obtained in healthy participants and TLE patients using GE2REC protocol were similar to meta-analytic LMN (see Chapter 3, they were not identical. Notably, some of the subcortical structures were not included among the ROIs such as the cerebellum and thalamus. As mentioned these structures play indispensable roles in language (see Chapter 1, Addendum 1.1) and temporal lobe seizures (thalamus, see Chapter 3, section 3.1.2). Moreover, they are a part of LMN that can be mapped with the GE2REC protocol (see Chapters 2 and 3 and Figure 3.4). Therefore, future studies could check the reproducibility of the presented findings and conclusions by using the individual LMN ROIs obtained in each participant using the GE2REC protocol.

#### 4.4.5 Conclusion - dynamics of LMN supporting language-memory integration

This chapter aimed to deepen our comprehension of the language-memory interaction by exploring the functional organization of its neural basis, the LMN. Although resting-state has been related to individual differences and various performances (Arnemann et al., 2015; Shen et al., 2018; van den Heuvel et al., 2009), our study joins others showing that it is also necessary to explore the network architecture during task performance to understand complex interactive functional networks that are the base of cognitive processing (Cole et al., 2014; Hearne et al., 2017; Schedlbauer & Ekstrom, 2019). Using a data-driven approach, we aimed to explore the changes in main functional networks and regions of LMN that are required when the context explicitly demands their collaboration.

Studying the differences between state-dependent LMN configurations revealed the key language and declarative memory subprocesses the network is trying to support with its adaptation. On the other hand, studying the reorganization in network state re-configuration in TLE patients allowed us to understand the supplementary processes language-memory interaction needs when the standard interface is not functional.

Our findings corroborate that LMN is indeed a dynamic network whose functional organization changes according to environmental demands and the condition of an individual (healthy vs. pathological).

When the task forces the language-memory interaction, the LMN of healthy individuals reconfigures through migration of key language and memory regions and segregation of the temporo-mesial module. This module corresponds well with the notion of language-memory interface (Duff & Brown-Schmidt, 2012) or the hippocampus as the connector

as conceptualized in the PMAT model (Ranganath & Ritchey, 2012). Therefore, this module could be essential for the language-memory interaction, binding the elements into flexible (re)constructions of representations (Olsen et al., 2012; Rubin et al., 2017). While lateral and mesial temporal regions enable state reconfiguration in healthy individuals, these regions show reduced flexibility in TLE. Specifically, in TLE, the LMN intrinsic-extrinsic reconfiguration manifests as an increase in segregation. Moreover, their extrinsic modules have connections that are shorter-distance than the ones in healthy participants. There are three main explanations for this reorganization of LMN state reconfiguration in TLE patients. First, the higher segregation could serve to specialize some specific functions (Bullmore & Sporns, 2012; Fornito et al., 2016) that act as a compensatory mechanism. Specifically, the segregation of the extrinsic “control” modules and the increase of DAN connector hubs in TLE when engaging in the recall task suggest that these patients rely more on cognitive control to integrate LMN during the extrinsic state. Second, modules with shorter intra-module connections could result from the loss of distal connections previously found in TLE (Englot et al., 2016; Liao et al., 2010; Roger, Pichat, et al., 2020) and a mechanism to reduce the wiring costs (Bullmore & Sporns, 2012; Fornito et al., 2016). Third, a higher number of modules could present a mechanism for preventing damage propagation throughout the network (Fornito et al., 2016). Finally, in the extrinsic LMN of TLE patients, the hippocampus does not segregate into a separate module but couples with the other regions of the declarative memory system, particularly regions of the semantic system. This may burden the regions of the semantic system with additional tasks (performed by temporo-mesial module in healthy individuals), which can manifest as memory and naming problems, typical for TLE patients (Allone et al., 2017; Bartha-Doering & Trinko, 2014; Tramoni-Negre et al., 2017).

So far in our work, we have mapped the LMN in healthy individuals, explored its reorganization in TLE patients, and investigated the functional organization of this network across states and conditions. We will now use the obtained findings to propose a model of the interaction between language and memory. Moreover, we will conclude this manuscript by discussing the potential use of this perspective and data to predicting the neurocognitive outcome for TLE patients undergoing surgery and present the ongoing and future studies.

**Box 4.3 Main Conclusions**

- LMN is a dynamic network with state- (intrinsic vs. extrinsic) and condition-dependent (healthy vs. pathological) organization.
- In healthy individuals, LMN reconfigures to extrinsic state through migration of key language and memory regions and segregation of the temporo-mesial module.
- The temporo-mesial module in HC could be acting as an interface between language and memory.
- In TLE, LMN reconfigures to extrinsic state through an increase in segregation.
- The reorganization of LMN state reconfiguration in TLE patients could be the result of (i) specialization of specific functions that serve as a compensatory mechanism; (ii) loss of distal connections in TLE; and (iii) prevention from damage propagation throughout the network.
- The absence of the extrinsic temporo-mesial module in TLE could be related to memory and naming problems, typical for TLE patients.
- TLE patients rely more on cognitive control to integrate LMN during the extrinsic state.

# Chapter 5

## General discussion

### Contents

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## 5.1 General synthesis and open questions

This thesis aimed to explore the interaction between language and memory from the cognitive neuroscience perspective. In doing so, the principal focus was language, while we were interested in the supporting role of memory. There are already many well-described language models that have received much empirical support (e.g., Binder & Desai, 2011; Hickok & Poeppel, 2007; Matchin & Hickok, 2020; Price, 2012). However, they are focusing on specific language processes, and most of them do not consider the communicative context. Thus, they do not account for how our knowledge, memories, beliefs influence our language processing. As discussed in the Introduction (Sections 1.1.1 and 1.3), cognitive systems are in constant interaction. Hence language relies on other systems for playing its demanding role in our everyday lives. In other words, language alone cannot actualize all of its functions and properties (e.g., allowing dislocation from time and space) in isolation but in cooperation with other functions. The connection between the language and declarative memory system is especially valuable because they share a domain - semantics. We were in particular interested in how this language-memory interaction is supported on the neural level.

Further evidence for language-memory interaction comes from the findings regarding temporal lobe epilepsy patients. The epileptogenic network of these patients is focused on the temporal lobe and is usually followed by hippocampal sclerosis. At first, the question was why these patients have problems both in language and memory domains if their memory center is damaged (hippocampus). However, a growing number of contemporary studies showed that this region and temporal lobe, in general, are the intersection of language and memory. Hence, the questions should be changed into how the language-memory interaction is reorganized in these patients if the main line of communication between them is damaged and what are the cognitive consequences. The goal of the REORG project within which this thesis was carried out was to provide answers to these questions and practical tools for the clinical practice. To that end, the GE2REC protocol was developed. It allowed us to examine language and memory in interaction across different memory processes and modalities.

Based on all of our findings (empirical, as well as the ones based on the literature review), we make the following general conclusions. Language-memory interaction relies on an extensive LMN fronto-temporo-parietal network also containing subcortical structures. The communication between language and memory is supported by the binding functions of the hippocampus. It is additionally supported through the control subnetworks, which becomes even more critical in TLE patients. This network is dynamic and reconfigures according to the state and environmental context (task). Its reconfiguration is based on the change of communication between different subnetworks that compose LMN as a meta-network. TLE patients show different intra- and interhemispheric reorganizations of this network, although their LMN generally includes similar regions as in healthy individuals. Moreover, its reorganization in TLE patients is reflected in a different reconfiguration between the state and external contexts. Overall, the mechanisms of LMN integration are changed in TLE.

To conclude this manuscript, we must answer the two final questions that we opened and set as the goals of our work (see section 1.9). First, what is the fundamental conclusion that we can make regarding the language-memory interaction? Second,

can this language memory interactive framework have practical utility for presurgical examination? Hence, the conclusions of this work are presented in Figure 5.5 after discussing these two questions.

## 5.2 Fundamental research contributions of language-memory approach

In the introduction of this manuscript (Chapter 1, Section 1.5), we presented two models - MUC and DP (Hagoort, 2005; Ullman, 2001) that, in different ways, take into account language and memory interaction to explain language functioning. In general, both models propose that declarative memory supports linguistic knowledge. Hagoort's model 2005 also includes the control component that manages attention and adapts the language to the current conversational context. However, these models do not fully address the broadness of language communicative function.

Communicative situations demand individuals to keep in mind the content of their message (their memories, knowledge, and beliefs) and the idea of what is shared between them and their interlocutors (what is their common ground Brown-Schmidt & Duff, 2016; Horton & Gerrig, 2016; Horton & Gerring, 2005). Hence, a model of language functioning that aims to include its communicative function and get close to everyday language use should address the relationship between language and declarative memory. In doing so, such a model should include both semantic and episodic declarative memory systems, as they are closely interdependent, continuously interacting, and partially overlapping (Duff et al., 2020; Irish & Vatansever, 2020; Renoult et al., 2019; Renoult & Rugg, 2020). We propose such a model based on our findings and inspired by previous models and proposals (e.g., Duff & Brown-Schmidt, 2012; Hagoort, 2016; Matchin & Hickok, 2020; Mesulam, 1990, 2000; Ranganath & Ritchey, 2012). Nevertheless, our proposal needs to be further verified. It is based on the small sample study whose findings remain to be replicated. Although contemporary studies usually use available large-scale datasets (such as Human Connectome Project, HCP, Barch et al., 2013), these data do not include a task that would resemble a communicative situation. The tasks used in HCP are set to delineate core functions, whereas we are interested in their interaction. Therefore, we base the model on the functional connectivity findings we obtained using the GE2REC protocol (see Chapter 2 for protocol description), more precisely, the sentence recall task for several reasons.

First, we decided to use the sentence recall task since it required a combination of language and memory. Although the other tasks incited the interaction of these functions, they did so less explicitly. Namely, participants were not instructed to memorize the words and sentences in the sentence generation task, so the encoding was implicit. While, in the recognition task, the participants were not asked to name the pictures, although this process happened automatically upon seeing a picture. Of course, sentence recall task merely mimics a part of everyday communication. It lacks the interlocutor, so the common ground is not directly included. However, the equipment availability and the study's clinical setting (see Chapter 2, section 2.1.4) limited the possibilities. Nevertheless, our task elicits the activation of the episodic memory system (see the

results of Chapters 2 and 3) that the common ground is relying on (among other systems, Brown-Schmidt & Duff, 2016).

Second, the difference in activation between healthy individuals and LTLE patients was the smallest for the recall task (see Chapter 3 and Figure 3.5). Although some of the patients in that study had pathological scores on neuropsychological tests, they were all generally capable of engaging and maintaining regular, fluent everyday communication (despite not remembering specific episodes or finding the right word occasionally). In other words, their language was still fulfilling its communicative function. Hence, we were interested in understanding how their LMN (the neural basis of the language-memory interaction) reorganizes to allow this functioning, despite the damage to one of the main parts of this network - the temporal lobe. In other words, we were interested in neural mechanisms that allow a person with a temporal lobe impairment to maintain communication, despite showing problems with the functions on which this communication is based when they are directly examined (i.e., showing reduced scores in tests of long-term memory or naming).

Third, in line with one of the guiding principles of this work (see Box 1.1), stating that cognitive processes are based on distributed networks of brain regions, we mainly based on the functional connectivity findings. In line with the connectomic perspective and GT, we will use the term module to refer to the group of regions that share a specific function during sentence recall. Moreover, although we will describe the underlying processes one by one, we do not intend to imply that they are happening linearly. Even though some processes are necessary prerequisites for others (e.g., a person needs to recognize a word before composing a sentence), we hypothesize that most of the essential processes are happening in parallel.

### 5.2.1 How are language and memory communicating to support our communication

Our language-memory interaction model<sup>1</sup> assumes that the neural basis of this interaction is the dynamic LMN<sup>2</sup>. The modular configuration of this network is similar in terms of segregation during intrinsic and extrinsic states, being flexible and requiring slight reconfiguration to be functionally effective in response to tasks (Mesulam, 2000; Schultz & Cole, 2016). We use the following communicative context for our model: Person A asks person B what (s)he told person C about a particular thing. Therefore, person B needs to remember and repeat something (s)he said about a particular thing. Once an individual tries to formulate a phrase based on previous experiences, the LMN reconfigures into its extrinsic state. This reconfiguration is mainly based on the "movement" of the regions located in (inferior and middle) frontal and (lateral and mesial)

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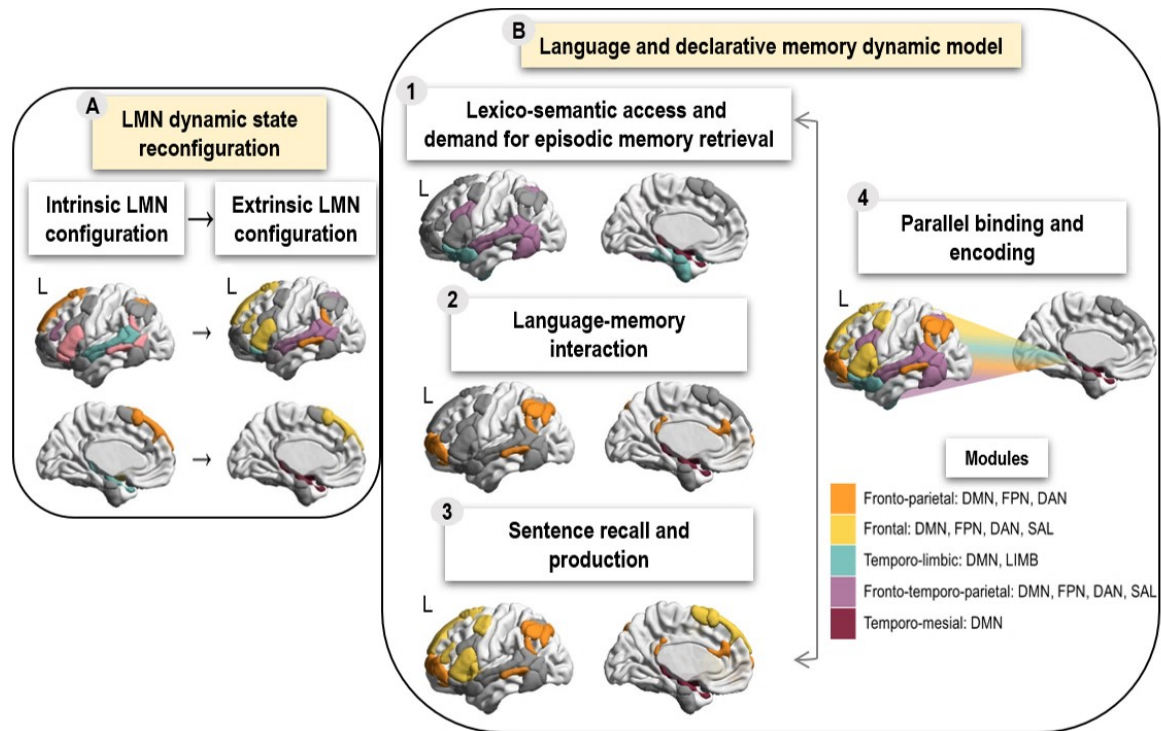
<sup>1</sup>Within the REORG project, another model was proposed that accounts for this interaction. The LUM model (Language/union/Memory, Roger et al., 2021) abandons the traditional cognitive-centric approach. It proposes that language and memory form a continuum that is composed of three fundamental dimensions Embodiment-Formulation-Internalization. It describes language and memory relationships through RSN interactions. Nevertheless, due to the complexity of the LUM model and somewhat different focus from the one of this work, this model will not be presented in more detail in this manuscript. The paper describing the LUM model is available on the following link - [10.31234/osf.io/p98n3](https://doi.org/10.31234/osf.io/p98n3).

<sup>2</sup>The presented model refers to individuals without neurological and psychiatric deficits.

temporal lobes (see Figure 5.1, Panel A). During sentence recall, language key regions join other modules according to task demands, while mesial temporal regions become an "interface" module engaged in episodic information extraction and binding it into a coherent experience (Cooper & Ritchey, 2020; Ranganath & Ritchey, 2012).

Specifically, when a person hears a cue word, a module should be formed that engages in "word recognition" and the start of the lexico-semantic search. We believe that this module should be extensive and resemble the fronto-temporo-parietal module found in our study (Figure 5.1, Panel B, Subpanel 1, Menenti et al., 2012; Price, 2012). This module should contain the majority of the ventral pathway regions. It would group pSTG engaged in the auditory-phonological network and following the ventral pathway MTG and IFG parts of the lexico-semantic network (Hickok & Poeppel, 2007; Middlebrooks et al., 2017; Price, 2012). In terms of RSN, this module should be composed of DMN regions that are connected with long-term memory (Buckner et al., 2008; Wirth et al., 2011), SAL regions that allow attentional focus on the heard word (Vossel et al., 2014) (Vossel et al., 2014), and DAN regions that guide a goal-directed lexico-semantic search (Dixon et al., 2017). However, we do not assume that the modules support clearly delineated processes (e.g., a module only engaged in semantics or phonology). Instead, parts of functional subnetworks or RSNs group into modules. Hence, the rest of the semantic network regions are distributed in other modules.

Relying on the PMAT model (Ranganath & Ritchey, 2012), we assume that there should be two modules resembling PM and AT systems from this model, both of which should contain some semantic network regions. First, there should be a module that provides a contextual scaffold through the "event knowledge" or thematic relations between entities. This module should group fronto-parietal regions. We indeed found a fronto-parietal module that resembled PM system and contained AG as one of the semantic hubs (Binder & Desai, 2011; Matchin & Hickok, 2020). The event features could be triggered in the parietal part of the fronto-parietal module since a person knows what episode (s)he is talking about. In the case of our study, for the recall task, we instructed participants to think about the sentence generation task, providing them thus with the context. Similarly, in our imaginary example, person A provides a context to person B in the question. In addition, following PMAT model (Ranganath & Ritchey, 2012), there should be a module supporting the "knowledge of entities" (Matchin & Hickok, 2020) that is "glued" on the contextual scaffold (Reagh & Ranganath, 2018). Such a module should group pOrb and anterior temporal regions (parts of the semantic system, Grande et al., 2012; Middlebrooks et al., 2017; Price, 2012) found as the temporo-limbic module in our research. We believe that the temporo-limbic module triggers the "demand" for the specific episodic retrieval related to the word recognized through its connection with the hippocampus.



**Figure 5.1:** Schematic representation of the model of language and declarative memory dynamic interaction based on LMN. Panel A shows state reconfiguration from intrinsic to extrinsic state during sentence recall. Only the regions that changed module (“movers”) are colored and the colors correspond to their modules for each state. Non-mobile regions (that remain in the same module) are presented in gray. Temporo-lateral module in rest divides into temporo-lateral and temporo-mesial modules in task that are engaged in semantic and episodic memory respectively. Fronto-temporo-parietal module found during rest includes language key-regions that separate during the task into modules that are engaged in lexico-semantic access, syntactic processing and sentence generation. Panel B shows cognitive processes recruited by the composite language and declarative memory function and the underlying LMN during the task. Within each subpanel we present language and declarative memory subprocesses and the corresponding modules presented in color. Fronto-temporo-parietal and temporo-limbic modules are engaged in lexico-semantic access while temporo-limbic module is also engaged in episodic retrieval (Subpanel 1). Hippocampo-amygdalar module is engaged in episodic retrieval and fronto-parietal module in concept access (Subpanel 2). Through the connection of hippocampo-amygdalar and fronto-parietal modules, the sentence is recalled and the information is transferred to working memory. Fronto-parietal and frontal modules are engaged in syntactic processing and sentence production (Subpanel 3). Hippocampo-amygdalar module can also access the information from all modules, combine it into a complete experience and perform encoding in parallel (Subpanel 4).

In line with the PMAT model (Ranganath & Ritchey, 2012; Reagh & Ranganath, 2018) and the proposition of the “language memory interface” (Duff & Brown-Schmidt, 2012), there should be a module composed of mesial temporal structures that performs the pattern completion by binding the information from the temporo-limbic and fronto-parietal modules. Through this process, the specific episode is retrieved and transferred to the working memory. This was observed as the temporo-mesial module in our research. The working memory module should group frontal, parietal, and

temporal regions (Wen et al., 2018). There should also be a positive increase in the interaction between DMN and FPN regions during memory retrieval (Vatansever et al., 2017). This again corresponds to the fronto-parietal module in our research composed of DMN and FPN regions.

In the introduction of this manuscript, we discussed the importance of the episodic buffer, a component of the working memory system, for fluid communication since it was supposed to bind and integrate information from working and long-term memory (see section 1.4.4 in Chapter 1). However, there are mixed findings in the literature concerning its neural substrate. While some suggest that it is based on the computations performed in the parietal lobe (Rugg & Vilberg, 2013; Wen et al., 2018), others investigated the hippocampus as the episodic buffer substrate (Twick & Levy, 2021). Seeing how essential the episodic buffer is on the cognitive plane for language-memory interaction, we must account for its neural substrate in proposing the neurocognitive model of this interaction.

To address this issue, we will give attention to the frontoparietal module. Namely, parietal regions, especially AG, are implicated in various cognitive functions (for a review, see Seghier, 2013). AG was proposed to be the hub region for both semantics (Binder & Desai, 2011; Matchin & Hickok, 2020) and episodic memory (Rugg & Vilberg, 2013; Spaniol et al., 2009). Its integrative role is widely acknowledged within the semantic perspective, and it is seen as integrating or binding the information from different modalities. However, its integrative role in episodic memory was somewhat overshadowed by the hippocampal binding role. Nevertheless, there are models trying to account for this integrative function of AG (Ramanan et al., 2018; Shimamura, 2011). Recently, Humphreys et al. (2021) proposed a unifying model based on both semantic and episodic oriented research, suggesting that AG enables an online dynamic buffering of multisensory spatiotemporally extended representations. Nevertheless, it remained somewhat unclear how it differs from hippocampal binding. Moreover, this also resembles a lot to the notion of the episodic buffer.

It seems that the novel proposition made by Twick and Levy (2021) fits well here. Namely, these authors proposed that the episodic buffer should be fractioned. They propose that what is termed episodic buffer actually included two cognitive processes – binding related functions and schema related functions. The hippocampus supports binding-related functions. On the other hand, the "schematic buffer" represents complex concepts and schemata. The network proposed to support this buffer comprises AG, MTG, and PFC (Twick & Levy, 2021), which corresponds well with our fronto-parietal module. Moreover, Ramanan et al. (2018) also contrasted hippocampal and AG functioning within episodic memory retrieval. They concluded that hippocampal binding is supporting the memory "crux" while AG supports the integration of the multimodal contextual details that provide the rich experience and "re-living the episode". The multisensory spatiotemporal dimension that is added by the fronto-parietal module is what makes the episode "re-lived" (Ramanan et al., 2018) and available to autonoetic awareness (Humphreys et al., 2021) and it is transformed into syntactic representation by the pMTG computations<sup>3</sup>.

In addition, there should be a module engaged in the speech production containing

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<sup>3</sup>The fronto-parietal module contained only pMTG region in our research, so we left out temporal from its name to avoid confusion with the FTP1 and FTP2 modules

the parts of the dorsal stream (Hickok & Poeppel, 2007; Monroy-Sosa et al., 2021). It was observed as the frontal module in our research that contained pTri, precentral and SMA among other regions (Figure 5.1, Panel B, Subpanel 3, Grande et al., 2012; Price, 2012). We believe that this module transfers syntactic representation into a linearized sequence (Matchin & Hickok, 2020) through the connections with fronto-parietal module.

Finally, even though the focus of this process is retrieval, the whole episode of retrieving is also being encoded. We propose that all through this process, the temporo-mesial module has access to information from all modules. This module binds the information into a complete experience and encodes the current episode in parallel (Figure 5.1, Panel B, Subpanel 4 Cooper & Ritchey, 2019; Ranganath & Ritchey, 2012).

Based on all presented, we propose that the temporo-medial buffer indeed supports binding the details of the episode "crux" based on the retrieved cue and the schema in the parietal part of the fronto-parietal module. Through the hippocampal mediation, the representation is sharpened into a representation of the specific event (Reagh & Ranganath, 2018). This representation becomes "multisensory spatiotemporally extended" and available for conscious awareness owing to fronto-parietal buffer (Humphreys et al., 2021). These representations allow individuals to reflect on them and make judgments (Humphreys et al., 2021). Therefore, we can assume that both buffers are necessary for acting in a communicative context (Figure 5.1, Panel B, Subpanel 2). The semantic-episodic integration is happening on the level of the hippocampus interface, while the shaping of the message with respect to the formed representations/context is happening on the level of fronto-parietal buffer.

We will now consider how this language-memory interactive approach could be of use in understanding cognitive deficits of TLE patients and their presurgical evaluation.

#### Box 5.1 Principal propositions of the proposed language and declarative memory model

- Proper communicative functioning relies on the integration of episodic (contextual, multisensory spatiotemporal representations) and semantic (conceptual) information;
- Language-memory communication happens on the representational level;
- Episodic buffer is essential for language-memory interaction
- These interactive processes are supported with the executive or control processes based on FPN, DAN, and SAL RSN networks.

### 5.3 Clinical contributions of language-memory approach

As presented in Chapter 3, TLE patients can show reorganization of cerebral networks due to their chronic illness and following surgery (Baciu & Perrone-Bertolotti, 2015;

Chang et al., 2017; M. K. Sidhu et al., 2013). Both of these reorganizations can be followed by reduced cognitive performance (Phuong et al., 2020; Sherman et al., 2011). We need to answer how our approach and findings can help us better understand these patients' cognitive dysfunctions, predict them, and provide a possible rehabilitation. Although our standard fMRI task-based analyses (Chapter 3) did not show reduced hippocampal activation in LTLE patients (Figure 3.5)<sup>4</sup>, which could have been expected based on their epileptogenic zones, the GT analyses (Chapter 4) showed that the integrative power of this structure is reduced in TLE patients during the task (Figure 4.6). As presented in the language-memory interaction model, the episodic buffer that relies on the hippocampus, supports semantic-episodic integration, and generally represents the interface between these functions (Duff & Brown-Schmidt, 2012; Tracy & Boswell, 2008; Twick & Levy, 2021). So what are the LMN compensatory mechanisms in TLE patients that support language-memory integration on the cognitive level when the standard interface is nonfunctional?

Our findings can seem somehow contradictory at first glance. The results of the standard fMRI analyses in Chapter 3 suggested that LTLE patients show reduced activation of the integrative hubs, especially those that belong to control networks. On the other hand, community structure findings in Chapter 4 suggest that these control network regions begin to have a more integrative role when a TLE patient engages in a task. We believe that these findings suggest that the reorganization mechanism within LMN is to base the LMN integration on other networks and regions with the capacity for integrative computations such as IFG, AG, and inferior temporal (Binder & Desai, 2011; Seghier, 2013). As in healthy individuals, AG in TLE also constitutes the fronto-parietal module, we proposed to act as the second episodic buffer (Twick & Levy, 2021). At the same time, IFG (pTri) and inferior temporal gyrus act like the hippocampus in healthy participants and segregate into a new module. Previous studies also found that language (semantic) and memory (episodic) retrievals can be additionally supported by the control network or processes when needed. For instance, Vatansever et al. (2021) found that weaker and less coherent experiences recruit control regions in healthy individuals. In their study retrieval of weakly associated semantic and weakly encoded episodic memory traces elicited the engagement of the areas in the left IFG and anterior insula. Performing network analyses on cognitive tests in TLE patients, Kellermann et al. (2016) similarly found that executive functions formed modules with other functions. Specifically, executive functions constituted one module with verbal and visual memory and one with language, intelligence, and nonverbal memory. These authors concluded that the interdependency between memory and executive functions and their relationship with different domains could serve as a possible pathway of reorganization of cognitive deficits. These and our findings can be related to the results presented in Roger's thesis (2020), also performed within the REORG project. Namely, analyzing cognitive profiles of TLE patients, she found that within the cognitive network, verbal executive scores (that were not pathological) were acting as connector hubs in RTLE patients, whereas these functions did not have such a significant role in LTLE patients. In the case of LTLE patients, the associative verbal memory was acting as the connector hub, even though it was pathological. In addition, RTLE had better cognitive

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<sup>4</sup>This result could also be the consequence of introducing the age regressor in the analyses since our control and TLE groups differed in age.



performance than LTLE patients. Considering that our fMRI task-based study (Chapter 3) only included LTLE patients, it would explain why we found reduced activation in the regions from the control networks. A possible critique could be that the results of the community structure analysis (Chapter 4) were under the influence of the RLTE patients. However, most of our sample in that study was composed of LTLE patients (11 LTLE vs. 5 RLTE).

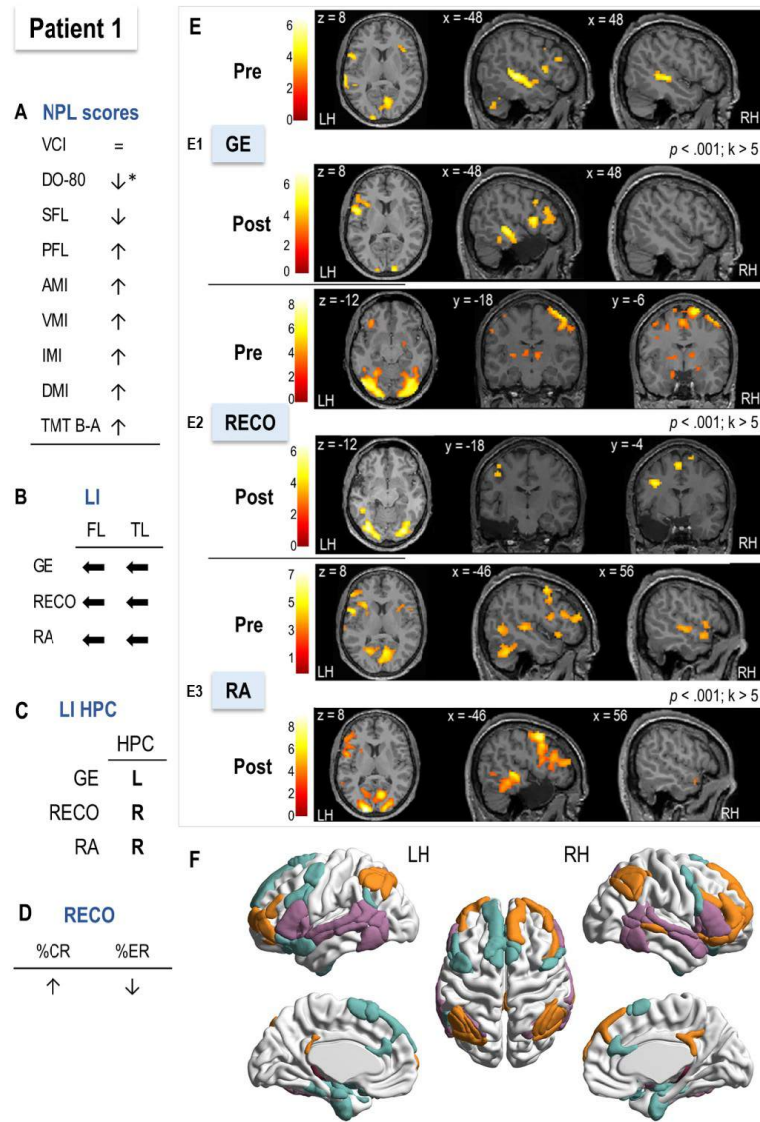
Since reduced segregation of cognitive domains in TLE patients would support higher alliance between functions (Kellermann et al., 2016), other cognitive domains could support the binding function that is weakened in these patients due to poorer hippocampal functioning. Therefore, the compensatory mechanism for which there is neural support is to rely on other networks and regions that can perform integrational computations. Our results suggest that these regions mainly belong to control networks (FPN and DAN). These findings lead to the conclusion that TLE patients could benefit from including the executive functions training in cognitive rehabilitation or prehabilitation plans. The goal would be to encourage patients to develop strategies based on the functions that should not decrease after temporal lobe surgery (or can even increase, Helmstaedter et al., 2018; Helmstaedter, 2013), and that are supported through the reorganizational mechanisms of LMN.

Improving working memory capacity was indeed found to help the improvement of different cognitive skills (Chein & Morrison, 2010). It was also shown that the intervention focusing on cognitive control (resolving of the information-processing conflict) influenced performance on both language (verb generation) and memory (recognition) tasks for which it was necessary to resolve a conflict among active competing representations (Hussey et al., 2017). However, the durability of found effects remains to be tested. In general, although cognitive rehabilitation can be helpful as a remedy for cognitive impairments in epilepsy patients, meta-analyses exploring the effects of these treatments provide limited empirical evidence for their efficacy and need further research (Farina et al., 2015; Mazur-Mosiewicz et al., 2015). The employment of various rehabilitation techniques and the individual adaptation to patients' needs could explain these results (Mazur-Mosiewicz et al., 2015). Despite limiting the possibility to compare results across studies, a rehabilitation/prehabilitation plan needs to be adapted to patients' individual characteristics although it should follow some standardized guidelines (for prehabilitation framework, see Baxendale, 2020). Related to that, to predict the postoperative risk of cognitive decline, a detailed picture of a patient's neurocognitive strengths and weaknesses needs to be made. This emphasizes the need for exploring language-memory interaction at the individual level. Indeed, Fedorenko (2021) recently highlighted the importance of individual-level analyses, not only for clinical practice, but for further advancement of cognitive neuroscience. She showed how group-level analyses can miss an effect due to low voxel-level overlap across individuals, underestimate the effect size and blur distinctions between functionally distinct areas in close proximity. Finally, in everyday clinical practice, a decision is made for the individual. Therefore, the question that poses is can our approach be informative on the individual level?

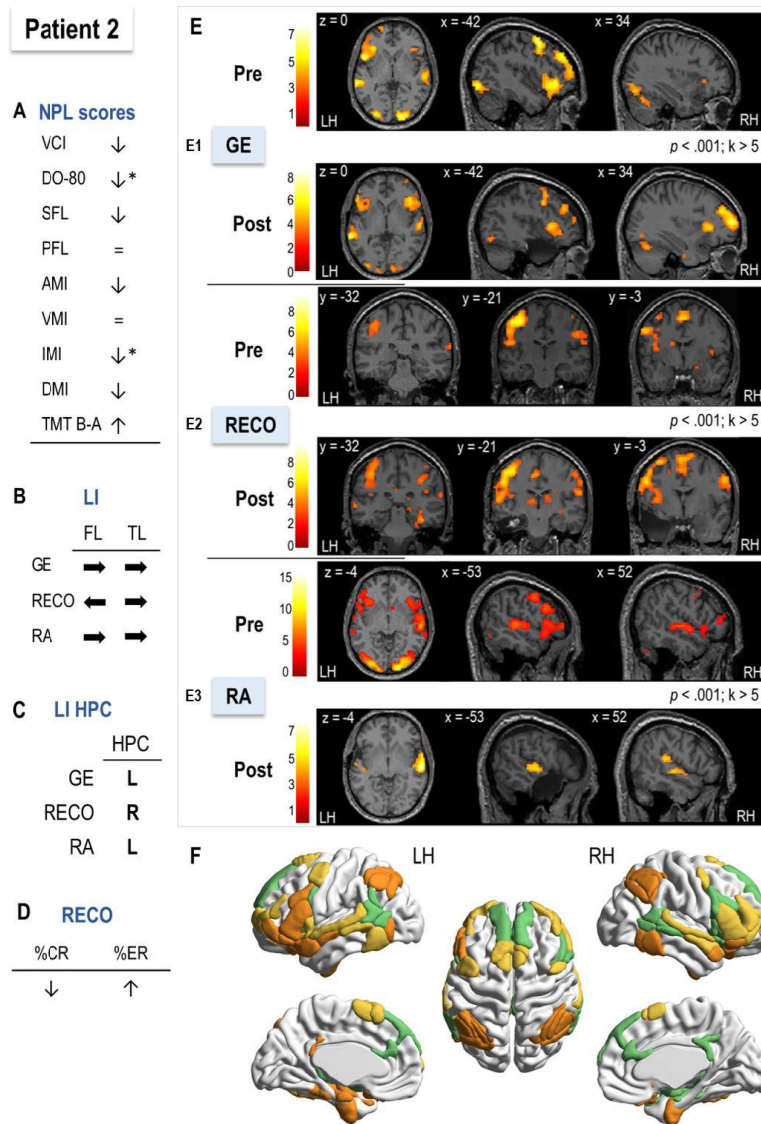
### 5.3.1 Perspectives: Individual-level applicability of the language-memory approach

To provide evidence-based conclusions regarding the utility of our approach in clinical practice, we are currently increasing the sample of patients whose LMN is mapped with our protocol before and after surgery. Hence, this research is still ongoing, and for that reason, it was not presented as a part of Chapter 3, in which we investigated LMN in LTLE patients. However, in line with the thesis objectives, we briefly present two mesial LTLE patients with HS who underwent left anterior temporal lobectomy. The presented data serve as an illustration of the perspectives of our work.

The seizures of the first patient (P1), a 28-year-old man, started at nine months (early onset of seizures), while the seizures of the second patient (P2), a 45-year-old male, started at 40 years of age (late onset of seizures). Both patients were pharmacoresistant and underwent surgery. Functional MRI, neuropsychological, and language investigations were a part of their preoperative and postoperative assessment. Demographic, clinical, neuropsychological, and functional activation of patients before and after surgery are presented in Table S2. The cognitive performance of P1 was better than P2 before surgery. Notably, his executive functioning was also better, as P2 showed pathological executive functioning. As in the study presented in Chapter 4, we analyzed the LMN modular architecture of these patients during the recall task of the GE2REC protocol. In terms of network architecture (Figures 5.2 and 5.3, Panels F), we found segregation of temporo-mesial module in P1, similarly to healthy participants (Chapter 4, Figure 4.4). Temporo-mesial module of P1 was composed of bilateral posterior hippocampi. The anterior parts were included in other modules, perhaps because they were nonfunctional. Moreover, the HDI values suggested that P2 had significant disruption of the inter-module connections ( $HDI = -0.46$ ), while the P1's HDI was similar to healthy individuals ( $HDI = 0.04$ ; see section 4.2.6 in Chapter 4 for the explication of this index). These results could be related to the better cognitive functioning of P1 before the surgery.



**Figure 5.2:** Illustration of individual application of the GE2REC in Patient 1 (P1) before and after surgery. (A) The postsurgical change of neuropsychological and language scores. (B) The postsurgical change of frontal and temporal lobes LIs. (C) Presurgical hippocampal LIs. (D) The postsurgical change of behavioral performance for the recognition task. (E) The functional MRI activation before and after surgery for each task (sentence generation, recognition, and recall, respectively) at a threshold of  $p < .001$  and  $k > 5$ . Activations were projected onto the normalized anatomical image of P1 before and after surgery. The color scale indicates the T value. (E) The modular architecture of LMN during RA task before surgery in P1. Each color represents one module. Arrows in A, B, and D indicate change direction (increase, decrease, shift to left or right) after surgery. Arrows in A marked with \* indicate a significant score decrease (using a 90% confidence interval). Abbreviations: NPL = neuropsychological and language assessment; VCI = standardized score of verbal comprehension index for verbal semantic memory (Wechsler, 2008); DO80 = standardized score for DO80 task (Deloche & Hannequin, 1997); SFL = semantic fluency, z score of performance on the task of categorical word generation (Godefroy & GREFEX, 2008); PFL = phonological fluency, z score of performance on the task of alphabetical word generation (Godefroy & GREFEX, 2008); AMI = standardized score of auditory memory (Wechsler, 2009); IMI = standardized score of immediate memory (Wechsler, 2009); DMI = standardized score for delayed memory (Wechsler, 2009); TMT B-A = standardized score of Trail Making Test B-A (Godefroy & GREFEX, 2008); LI = lateralization index; FL = frontal lobe; TL = temporal lobe; HPC = hippocampus; GE = sentence generation with implicit encoding; RECO = recognition of items; RA = recall; LH = left hemisphere; RH = right hemisphere.



**Figure 5.3:** Illustration of individual application of the GE2REC in Patient 2 (P2) before and after surgery. (A) The postsurgical change of neuropsychological and language scores. (B) The postsurgical change of frontal and temporal lobes LIs. (C) Presurgical hippocampal LIs. (D) The postsurgical change of behavioral performance for the recognition task. (E) The functional MRI activation before and after surgery for each task (sentence generation, recognition, and recall, respectively) at a threshold of  $p < .001$  and  $k > 5$ . Activations were projected onto the normalized anatomical image of P2 before and after surgery. The color scale indicates the T value. (E) The modular architecture of LMN during RA task before surgery in P2. Each color represents one module. Arrows in A, B, and D indicate change direction (increase, decrease, shift to left or right) after surgery. Arrows in A marked with \* indicate a significant score decrease (using a 90% confidence interval). Abbreviations: NPL = neuropsychological and language assessment; VCI = standardized score of verbal comprehension index for verbal semantic memory (Wechsler, 2008); DO80 = standardized score for DO80 task (Deloche & Hannequin, 1997); SFL = semantic fluency, z score of performance on the task of categorical word generation (Godefroy & GREFEX, 2008); PFL = phonological fluency, z score of performance on the task of alphabetical word generation (Godefroy & GREFEX, 2008); AMI = standardized score of auditory memory (Wechsler, 2009); IMI = standardized score of immediate memory (Wechsler, 2009); DMI = standardized score for delayed memory (Wechsler, 2009); TMT B-A = standardized score of Trail Making Test B-A (Godefroy & GREFEX, 2008); LI = lateralization index; FL = frontal lobe; TL = temporal lobe; HPC = hippocampus; GE = sentence generation with implicit encoding; RECO = recognition of items; RA = recall; LH = left hemisphere; RH = right hemisphere.

Since both patients had surgery of the dominant hemisphere and were cognitively unimpaired preoperatively (Table D.1), according to previous studies, they were at greater risk of postoperative cognitive decline (Busch et al., 2018; Strandberg et al., 2017). Although the surgery was successful for both patients as they became seizure-free, they "paid a different cognitive price" (Baxendale & Thompson, 2018), as P2 showed a higher cognitive decline. Indeed, P1 showed a decrease in naming performance even if it remained within the norm and a slight decrease in semantic fluency score<sup>5</sup>. On the other hand, after surgery, P2 suffered a significant decrease in naming performance with a pathological score, a significant decline of immediate memory score, and a slight decrease of delayed and auditive memory indices (Figure 5.3, Table D.1).

The late ASO could explain the poorer negative cognitive outcome of P2 after surgery, in agreement with previous findings reporting that seizures occurring later in life are more detrimental for memory and for naming after temporal surgery (Dupont, 2015). However, the naming decline was greater in P1 than in P2 (even if values are within norms), which could be explained by resectioning of the patients' individual LMNs identified preoperatively using GE2REC. The resected areas of P1's and P2's preoperative LMN included superior temporal region and temporal pole in the ventral pathway and the semantic network (Binder & Desai, 2011; Middlebrooks et al., 2017; Monroy-Sosa et al., 2021; Price, 2012). Similarly, You et al. (2019) showed that resection of activated areas in the anterior temporal region predicted the postoperative decline for naming. However, in P1, the resected area also included left mesial temporal regions that were engaged in sentence generation and recognition preoperatively.

P2 showed greater right-hemispheric involvement after surgery, as revealed by sentence generation and recall tasks, in line with previous findings on reorganization patterns (Bonelli et al., 2012; Foesleitner et al., 2021). In the P2 case, the reorganization was not cognitively efficient, possibly related to weaker coupling between left and right frontal regions (Bonelli et al., 2012; Foesleitner et al., 2021) probably induced by late ASO. Indeed, seizures occurring late in life do not provide sufficient time for an efficient reorganization. Consequently, the right-hemisphere activation may still be an "unbeaten path" and cognitively inefficient (Dulay & Busch, 2012; Dupont, 2015).

As mentioned, establishing the functionality of the hippocampal structure is essential in the preoperative assessment of mesial TLE patients. Since hippocampal activation is difficult to obtain due to signal distortion (Buck & Sidhu, 2020; Haag & Bonelli, 2013; Powell & Duncan, 2005), and as the asymmetry of memory function was found to be more valid than the absolute activity in predicting the postoperative outcome (Milian et al., 2015), we focused on the hippocampal lateralization. Similar to previous studies (Dupont, 2015; Powell et al., 2008), P2, who relied more on the ipsilateral hippocampus than the contralateral across different memory processes and materials, had more significant cognitive decline than P1 who relied less on the ipsilateral hippocampus.

Nevertheless, although our findings can be related to observed preoperative and postoperative cognitive functioning and show that studying language-memory interaction on the individual level can be meaningful, the exact predictive power of our approach remains to be tested in a larger sample. The goal of the predictive studies and models

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<sup>5</sup>The significance of the change was calculated as the reliable change indices at 90% confidence interval (Baxendale & Thompson, 2005; Morley, 2017).

should be to assess the risk of cognitive decline after the surgery and inform patient counseling (Baxendale, 2020; Busch et al., 2021). Advances in the computing and machine learning fields showed their value in identifying and diagnosing diseases and designing timely and tailored preventions (Prosperi et al., 2020). However, in doing so, machine learning approaches are emulating human intelligence (El Naqa & Murphy, 2015), or in our case, the everyday work of physicians (neurologists and neurosurgeons) who are set to decide if a given patient should undergo temporal lobe surgery. Notably, this decision is based on a comprehensive diagnostic evaluation that considers multimodal data (Kanner et al., 2020; Memarian et al., 2015). Even the presented patients' neuroimaging results (P1 and P2) could not be interpreted without associating them with the patient's "clinical picture" (including their demographic, clinical characteristics, and cognitive functioning).

Regardless of the employment of a more ecological fMRI protocol that accounts for cognitive interaction, one type of data cannot suffice for understanding a patient's cognitive functioning, predict postsurgical outcomes, or design a potential rehabilitation/prehabilitation. This brings us to another perspective direction of our work - multimodal integration.

### 5.3.2 Perspectives: Using multimodal data to predict surgical outcomes

Studies set to predict surgical outcomes in TLE patients have focused on structural, functional, electrographic, clinical, neuropsychological variables and their combinations to predict seizure freedom after the surgery (Armañanzas et al., 2013; Memarian et al., 2015). Others looked for cognitive phenotypes (Baxendale & Thompson, 2020; Reyes et al., 2020) and classes of TLE patients based on the morphology of temporal structures (Bernhardt et al., 2015), searching for their diagnostic utility in predicting postsurgical outcomes. In line with one of the guiding principles of this thesis that interaction of cognitive processes supports behaviors (see Box 1.1.3), within the REORG project, Roger et al. (2021) recently showed the exact neuropsychological indices of language, memory, and executive functions that can globally predict surgery outcomes regarding seizure freedom and neuropsychological functioning. Although these results are promising, as we mentioned, our final goal is to combine different types of neuroimaging, clinical, behavioral, and neuropsychological data. This multimodal integration should help to detect the patterns that could be of potential use in clinical practice. The algorithms or nomograms obtained that way should serve as a tool for clinicians to make predictions regarding postoperative changes and implement prehabilitation (Baxendale, 2020). For instance, in a recent paper, Busch et al. (2021) provided models and nomograms predicting delayed verbal memory outcomes after temporal lobe resection combining demographic, clinical, and neuropsychological data. Their models had excellent predictive accuracy. However, their models did not include functional MRI data. Since our work is done from the cognitive neuroscience framework, in line with its goal of connecting cognitive and cortical networks (Gazziniga et al., 2014), we believe it is necessary to address the functionality of cortical networks.

It should be highlighted that this line of our work is also ongoing. It depends on the number of patients in our sample that will undergo surgery. For that reason, these

findings are not presented as a separate chapter, but rather as an illustration of the other perspective line of our work.

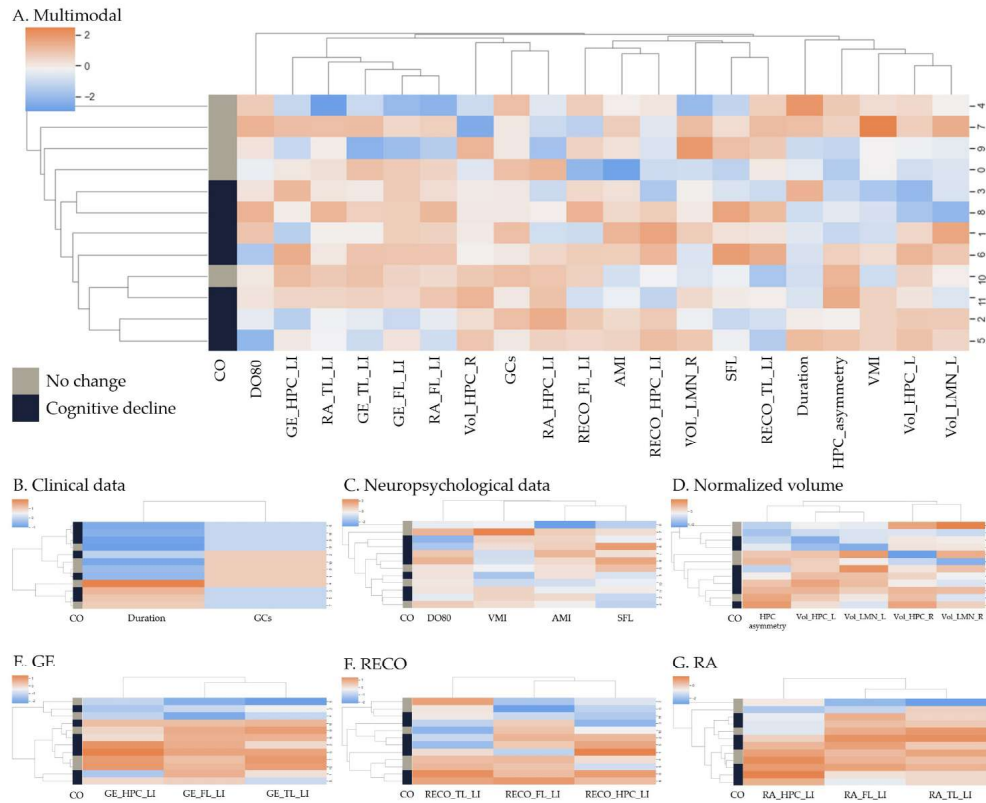
In this study, we include clinical, neuropsychological, anatomical volume<sup>6</sup> and fMRI data. Nevertheless, the available data (12 LTLE patients) allowed us to perform preliminary analyses. Patients were categorized as showing postsurgical cognitive decline if they significantly decreased on at least two language and/or memory tests after surgery. The significant change was calculated as reliable change indices at an 80% confidence interval (Baxendale & Thompson, 2005; Morley, 2017). Presenting our data through dendrograms (Figure 5.4) based on the euclidean distances, patients are grouped the best regarding their postsurgical cognitive outcome when all the modalities are included. Despite not finding two separated clusters, using all available modalities (Panel A of figure 5.4), patients with favorable postsurgical cognitive outcomes tend to be less similar to those with less favorable outcomes (except one patient).

However, in this pilot study, variables were selected based on the available data in our patient sample. For instance, HS, which is related to the postsurgical outcome (Busch et al., 2021), was not chosen because its variability in our sample was very low. Moreover, the number of selected variables was limited by the number of participants. This also opens an essential question of database dimensionality. Namely, numerous factors need to be considered when planning a surgery (Memarian et al., 2015), which translates into a high number of variables that should be taken into a model. Therefore, there is a risk of having more features than observations, leading to overfitting or finding the specific patterns for the training data that cannot be generalized (Calesella et al., 2020).

For the reasons stated, we take the presented findings as preliminary, serving only to illustrate the perspectives of our work. We need a larger sample for future work on multimodal prediction of postsurgical cognitive outcomes in TLE patients. We plan to use a machine learning approach and adopt different regularization methods (e.g., least absolute shrinkage or selection operator - LASSO) or dimensionality reduction techniques (Calesella et al., 2020; Mwangi et al., 2014). Also, our selection of neuropsychological tests and measures is site-specific (i.e., CHU Grenoble) and bound to our GE2REC protocol. Hence, as Busch et al. (2021) pointed out, the generalizability of our future work could be limited. Nevertheless, the protocols and analysis pipelines developed within the REORG project are freely available.

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<sup>6</sup>The volume-based analyses for this work are performed as a part of Fabricio Dutra's thesis within the REORG project. Using ANTs pipeline (Tustison et al., 2014) and patients' T1-weighted images, normalized volumes were calculated as the ratio between the volume of selected regions of interest (LMN and specifically the hippocampus) and total intracranial volume. Laurent Torlay produced the dendrograms.



**Figure 5.4:** Illustration of the perspective work regarding application of multimodal data for post-operative cognitive outcome prediction in TLE patients. Dendrograms present grouping of patients (left column of each dendrogram) based on their similarity using multimodal data (A), or each type of data separately, i.e., clinical (B), neuropsychological (C), normalized volume (D), and fMRI based on GE2REC tasks (E, F, G). Abbreviations: CO = cognitive outcome after surgery; Duration = epilepsy duration; GCs = generalized crises; DO80 = standardized score for French version of naming task (Deloche & Hannequin, 1997); SFL = semantic fluency, z core of performance on the task of categorical word generation (Godefroy & GREFEX, 2008), AMI = standardized score of auditory memory (Wechsler, 2009); VMI = standardized score of visual memory (Wechsler, 2009); HPC = hippocampus; LMN = language and memory network; FL = frontal lobe; TL = temporal lobe; LI = lateralization index; GE = sentence generation with implicit encoding; RECO = recognition of items; RA = recall.

## 5.4 General conclusion

In concluding this work, we will return to the first presented notion - [knowledge development through interaction](#). Just as one discipline was not sufficient to understand complex phenomena, we believe that complex phenomena cannot be understood if we remain focused on one isolated function or domain. Therefore, in this thesis, we have tried to understand better language “in its full glory” (Hagoort, 2013) based on the interactions between language and memory, research and clinic.

Cognitive neuropsychology is set to map cognitive networks onto cortical networks. We joined this aim by focusing specifically on the interaction between language and declarative memory. In our work, we sought to combine several modern concepts of cognitive neuropsychology. First of all, we based on the notion of networks in terms



of cognitive processes and their cerebral substitutes. We tried to gain a deeper understanding of the language function, exploring how it communicates with declarative memory function to meet all the requirements of everyday life. Moreover, we relied on recent findings and perspectives that abandon the sharp division between semantic and episodic memory and propose their interdependence and connection. Finally, we pointed out the practical importance of using multimodal data. As far as conditions allowed, we tried to use as many different modalities as possible in our research, although our findings are primarily based on fMRI data. Conclusions of our work is presented in Figure 5.5 in relation to the overview of the thesis provided in Figure 1.7 in Chapter 1.

Based on our findings, we proposed a neurocognitive model of language-memory interaction that can be summed up as follows. Within communicative context, declarative memory supports language so that we can dislocate from time and space in our conversation and shape our message so that it is comprehensible to our interlocutors. Our research showed that this language and memory interaction is based on a vast and dynamic network. The crucial interactive processes are happening on the “episodic buffer” level - one based on the mesial temporal structures and another on the fronto-parietal network. Based on these buffers, semantic and episodic elements are binded into experience and representations that shape our utterances. This relationship becomes even more evident when the LMN of TLE patients is explored since these patients have reduced functionality of the standard hippocampal buffer. Therefore, their LMN reorganizes. The other regions within the declarative memory system take over the functions of the damaged region, and cognitive control systems engage more in network integration. Consequently, TLE patients have episodic memory and/or lexico-semantic retrieval (naming) deficits.

As much as our findings provided some answers, they also opened several possible lines of future research. First of all, the proposed model of language-memory interaction during the retrieval needs to be further replicated and validated. The question for future research is whether the reconfiguration mechanisms of LMN are the same for different tasks. In other words, does its reconfiguration always depend on the movement of the temporal and frontal regions? Secondly, we assume that our sentence recall task resembles the behavior in the conversational context. However, this assumption needs to be empirically tested. For instance, the recall task can be compared with a task in which an individual needs to consider the interlocutor when planning and expressing a message. Second, as mentioned, this work also aimed to have practical implications for presurgical evaluation. We already outlined the perspectives regarding this line of work - testing the approach on an individual level and finding the algorithm that quantifies the risk of cognitive decline following temporal lobe surgery by basing on multimodal data. In addition, in our future work, we also need to further explore the practical clinical utility of examining the reconfiguration and reorganizational mechanisms of LMN of an individual patient. Furthermore, the exact added value of the language-memory interactive approach should be tested by comparing it with standard clinical protocols for language and memory. These and other open questions are presented in Figure 5.5. Finally, by connecting two functions (language and memory) and fields (research and clinic), our work can face numerous critiques from the perspective of researchers focused on each of these functions and/or domains. We acknowledge that our work requires

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significant further improvements and validation. In line with that, Figure 5.5 summarizes the limitations of each line of our work and proposes possible solutions. Therefore, the presented work and provided interpretations merely present the first step towards novel conceptualizations, and we welcome all additional critiques and hope they will guide us towards a more thorough understanding of human behavior's neurocognitive dynamics.

Conclusions based on the literature review (Ch. 1)	Dynamic language-memory interaction is supported by a joint language and memory network - LMN	TLE patients have reorganized LMN since its key regions are affected by this disease which results in cognitive difficulties in these domains	Exploring the interaction of cognitive functions could have both <u>practical clinical</u> and <u>fundamental</u> implications
Chapters in which the topic is discussed	Ch. 2, Ch. 4, Ch. 5	Ch 3, Ch 4, Ch 5	Ch 5
General conclusion	<p>Interactive language-memory tasks map LMN as a broad fronto-temporo-parietal network.</p> <p>LMN also includes subcortical structures.</p> <p>LMN can be mapped on individual and group level.</p> <p>LMN is dynamic and reconfigures across states and with respect to environmental demands.</p> <p>Language-memory interaction is based on episodic buffers – mesial temporal and fronto-parietal.</p>	<p>LTLE patients activate an LMN that generally resembles one of the healthy individuals.</p> <p>LTLE patients show higher variability in LMN lateralization than healthy individuals.</p> <p>Temporal mesial regions of TLE patients show poorer integrative properties compared to healthy individuals.</p> <p>LMN of TLE patients shows higher segregation during task execution than healthy individuals.</p> <p>In the absence of functioning temporal mesial interface, control networks will increase their support of LMN integration.</p>	<p>Multimodal data provides a better grouping of patients based on their cognitive surgical outcome.</p> <p>The overlap between activated LMN and the resected area seems to be related to postsurgical cognitive outcome.</p> <p>The language-memory interactive approach can inform rehabilitation/prehabilitation planning.</p> <p>Functional declarative memory is necessary for proper communication.</p> <p>The interaction of language and memory is achieved through episodic buffers that are supported by mesial temporal regions and fronto-temporal module.</p>
Novelty	<p>Exploring the functions in interaction</p> <p>Exploring the reconfiguration between the states</p>	<p>Exploring the reorganization of network reconfiguration</p> <p>The already known hippocampal paradox was shown to be related to resting state and non-functional</p>	<p>Using cognitive interaction in presurgical planning instead of basing on each function in isolation</p> <p>Connecting different existing models of language and memory into one</p>
Limitations and critique	<p>Weaker hippocampal activation, especially at the individual level</p> <p>The current version of the GE2REC protocol does not allow us to verify if participants really recalled the sentences and what type of sentences they generated (semantic or episodic-based)</p> <p>Absence of the subcortical structures in the LMN community structure analysis</p> <p>LMN community structure analyses were based on the hypothetical network and not the LMN a participant actually activates</p>	<p>TLE patient sample was very variable regarding demographic, clinical, and neuropsychological characteristics</p> <p>Limited evidence for the efficiency of reorganization (due to absence of significant correlations with neuropsychological scores)</p> <p>Absence of the evidence on reorganization mechanisms using standard fMRI analyses probably due to small sample and age regressor</p> <p>Analyses regarding cognitive efficiency using ROI data are close to localizationist paradigm</p>	<p>Absence of subcortical structures from the model of language-memory interaction</p> <p>It is difficult to conclude about the clinical utility of the protocol since patients did not perform other protocols</p> <p>In the illustration of multimodal prediction, there were no network parameters</p> <p>There is an overfit risk for the potential predictive model using multidimensional data, which would limit its generalizability</p>
Open question and perspectives	<p>Are the reconfiguration mechanisms of the LMN network the same for different tasks?</p> <p>Is the state reconfiguration of other networks involving temporal regions based on their flexibility? Or is it the specificity of the LMN?</p> <p>The modular architecture of the LMN should be verified in other participants and tasks</p> <p>Adding the questionnaire at the end of GE2REC would allow analyzing sentences participants produced and their recall</p> <p>Community structure analyses should be performed based on the each participants individual LMN</p> <p>Conclusions based on group-level analyses should be verified using individual-subject analyses</p>	<p>Is there a difference in LMN modular architecture between LTLE and RTLE?</p> <p>A larger sample of TLE patients should be used in order to explore the cognitive efficiency of the observed reorganization</p> <p>Results should be verified in TLE and HC groups that are age equivalent</p> <p>A parameter describing network (re)organization should be found which would allow to quantify its efficiency</p> <p>Community structure analyses of LMN should be adapted for the clinical setting</p>	<p>Added-value of the language-memory interactive approach needs to be tested in comparison to standard clinical protocols</p> <p>Multimodal prediction of the postsurgical cognitive outcome in TLE patients needs to be tested in a larger sample</p> <p>The practical clinical utility of the LMN reconfiguration and its reorganization remains to be determined</p> <p>The predictive model could benefit of including the indicators such as epilepsy acceptance, surgery acceptance, and available social support</p>

# Appendix A

## Chapter 2 Supplementary material

TABLE A.1: Activated regions for one participant for GE, ENCO, RECO and RA. The number of voxels in the cluster (k), the x, y, and z coordinates in millimeters, the anatomical region according to AAL atlas (Tzourio-Mazoyer et al., 2002), the Brodmann Area (BA), and the T value are indicated for each peak. All activations were obtained at  $p < .05$  corrected except for those with asterisks in the table ( $*p < .001$  uncorrected).

Abbreviation: GE = Sentence Generation.

Contrast	k	x (mm)	y (mm)	z (mm)	AAL	BA	T
GE [Sentence generation vs. Control]	<b>198</b>	<b>-54</b>	<b>11</b>	<b>20</b>	<b>Frontal_Inf_Oper_L</b>	<b>45</b>	<b>10.18</b>
		-54	17	23	Frontal_Inf_Tri_L		7.87
		-42	38	29	Frontal_Mid_2_L		5.08
	<b>288</b>	<b>-3</b>	<b>11</b>	<b>53</b>	<b>Supp_Motor_Area_L</b>		<b>9.59</b>
		-3	23	38	Frontal_Sup_Medial_L		6.63
		-12	17	47	Frontal_Sup_L		5.89
		-6	23	35	Cingulum_Mid_L	32	5.83
	<b>135</b>	<b>-48</b>	<b>-1</b>	<b>47</b>	<b>Precentral_L</b>		<b>9.31</b>
		-51	-7	41	Postcentral_L		6.91
	<b>91</b>	<b>-42</b>	<b>20</b>	<b>-19</b>	<b>Temporal_Pole_Sup_L</b>		<b>7.07</b>
		-48	26	-7	Frontal_Inf_Orb_2_L		5.68
	<b>79</b>	<b>-48</b>	<b>-28</b>	<b>-4</b>	<b>Temporal_Mid_L</b>		<b>7.00</b>
	<b>21</b>	<b>-60</b>	<b>-58</b>	<b>2</b>	<b>Temporal_Mid_L</b>		<b>6.99</b>
	<b>29</b>	<b>-21</b>	<b>41</b>	<b>-19</b>	<b>Frontal_Mid_Orb_L</b>	<b>11</b>	<b>6.86</b>
	<b>41</b>	<b>-33</b>	<b>17</b>	<b>8</b>	<b>Insula_L</b>		<b>6.83</b>
		-39	29	2	Frontal_Inf_Tri_L		4.85
	<b>83</b>	<b>30</b>	<b>-88</b>	<b>-4</b>	<b>Occipital_Inf_R</b>	<b>18</b>	<b>6.65</b>
		24	-88	-4	Lingual_R		6.41
	<b>13</b>	<b>45</b>	<b>38</b>	<b>32</b>	<b>Frontal_Mid_2_R</b>		<b>5.97</b>
	<b>22</b>	<b>-45</b>	<b>-37</b>	<b>53</b>	<b>Parietal_Inf_L</b>	<b>40</b>	<b>5.73</b>
	<b>12</b>	<b>42</b>	<b>-61</b>	<b>-34</b>	<b>Cerebelum_Crus1_R</b>		<b>5.12</b>
	<b>216</b>	<b>-48</b>	<b>-7</b>	<b>44</b>	<b>Precentral_L</b>		<b>9.48</b>
	<b>183</b>	<b>-54</b>	<b>5</b>	<b>23</b>	<b>Postcentral_L</b>		<b>8.23</b>
	-51	29	23	Frontal_Inf_Tri_L	46	5.72	
	-54	14	20	Frontal_Inf_Oper_L		7.62	
<b>190</b>	<b>-3</b>	<b>11</b>	<b>53</b>	<b>Supp_Motor_Area_L</b>	<b>6</b>	<b>6.87</b>	
	-15	17	47	Frontal_Sup_L		5.63	
<b>52</b>	<b>57</b>	<b>-28</b>	<b>2</b>	<b>Temporal_Sup_R</b>	<b>22</b>	<b>6.19</b>	
<b>248</b>	<b>30</b>	<b>-61</b>	<b>-25</b>	<b>Cerebelum_6_R</b>		<b>6.06</b>	
	9	-88	-7	Lingual_R		5.89	

ENCO  
[Correct  
vs.  
Incorrect]

		36	-67	-31	Cerebelum_Crus1_R		5.01
	<b>11</b>	<b>-57</b>	<b>-58</b>	<b>2</b>	<b>Temporal_Mid_L</b>		<b>6.00</b>
	<b>75</b>	<b>15</b>	<b>-79</b>	<b>-49</b>	<b>Cerebelum_7b_R</b>		<b>5.91</b>
		12	-67	-52	Cerebelum_8_R		4.83
		15	-79	-43	Cerebelum_Crus2_R		5.31
	<b>77</b>	<b>-57</b>	<b>-40</b>	<b>20</b>	<b>Temporal_Sup_L</b>		<b>5.88</b>
		-48	-31	-1	Temporal_Mid_L	21	5.23
	<b>29</b>	<b>18</b>	<b>-97</b>	<b>17</b>	<b>Occipital_Sup_R</b>	<b>18</b>	<b>5.34</b>
	<b>11</b>	<b>-18</b>	<b>-13</b>	<b>-13</b>	<b>Hippocampus_L</b>	<b>28</b>	<b>5.13</b>
		-15	-22	-16	ParaHippocampal_L		3.56*
	<b>13</b>	<b>-21</b>	<b>-76</b>	<b>-49</b>	<b>Cerebelum_7b_L</b>		<b>5.05</b>
	<b>37</b>	<b>24</b>	<b>-13</b>	<b>-13</b>	<b>Hippocampus_R</b>		<b>3.79*</b>
		18	-10	-19	ParaHippocampal_R	34	3.13*
	<b>4939</b>	<b>-30</b>	<b>-76</b>	<b>-19</b>	<b>Cerebellum_6_L</b>	<b>19</b>	<b>15.14</b>
		24	-82	-16	Fusiform_R		13.39
		-33	-70	-16	Fusiform_L		12.97
		21	-76	-10	Lingual_R	18	11.39
		-33	-76	-22	Cerebellum_Crus1_L		12.56
		45	-67	-10	Temporal_Inf_R		9.17
		12	-94	23	Cuneus_R	19	5.43
		21	-49	-22	Cerebellum_4_5_R		8.28
		-24	-46	-22	Cerebellum_4_5_L		7.56
		-42	-49	-16	Temporal_Inf_L		5.69
		-39	-73	-10	Occipital_Inf_L		12.35
		39	-73	-13	Occipital_Inf_R		11.62
	<b>1979</b>	<b>-24</b>	<b>-55</b>	<b>53</b>	<b>Parietal_Sup_L</b>		<b>9.36</b>
		-54	-1	41	Precentral_L	6	8.85
		-54	-16	41	Postcentral_L	4	6.05
		-54	-25	44	Parietal_Inf_L		6.02
		-45	20	23	Frontal_Inf_Tri_L		6.1
		-45	8	26	Frontal_Inf_Oper_L		7.57
		-42	41	26	Frontal_Mid_L		5.36
		-24	-4	56	Frontal_Sup_L		5.37
		-48	-34	26	SupraMarginal_L		7.22
	<b>174</b>	<b>24</b>	<b>-67</b>	<b>56</b>	<b>Parietal_Sup_R</b>	<b>7</b>	<b>8.35</b>
		30	-67	32	Occipital_Mid_R		5.91
	<b>84</b>	<b>57</b>	<b>8</b>	<b>32</b>	<b>Precentral_R</b>		<b>7.52</b>
		45	8	26	Frontal_Inf_Oper_R		7.20
	<b>179</b>	<b>0</b>	<b>11</b>	<b>50</b>	<b>Supp_Motor_Area_L</b>		<b>7.31</b>
		6	14	50	Supp_Motor_Area_R	6	5.36
	<b>74</b>	<b>-30</b>	<b>-70</b>	<b>-55</b>	<b>Cerebelum_7b_L</b>		<b>6.39</b>
		-36	-58	-49	Cerebelum_8_L		6.34
	<b>11</b>	<b>42</b>	<b>23</b>	<b>17</b>	<b>Frontal_Inf_Tri_R</b>		<b>6.11</b>
	<b>33</b>	<b>45</b>	<b>35</b>	<b>32</b>	<b>Frontal_Mid_R</b>		<b>6.01</b>
	<b>26</b>	<b>-30</b>	<b>20</b>	<b>5</b>	<b>Insula_L</b>		<b>5.76</b>
	<b>36</b>	<b>36</b>	<b>-4</b>	<b>65</b>	<b>Frontal_Sup_R</b>		<b>5.65</b>
		27	2	68	Frontal_Sup_R		5.63
		42	-1	56	Frontal_Mid_R		5.12
	<b>15</b>	<b>27</b>	<b>38</b>	<b>-16</b>	<b>Frontal_Mid_Orb_R</b>		<b>5.38</b>
	<b>37</b>	<b>-21</b>	<b>-1</b>	<b>-16</b>	<b>Amygdala_L</b>		<b>4.12*</b>
		-18	-13	-13	Hippocampus_L		3.55*
	<b>386</b>	<b>-21</b>	<b>-100</b>	<b>2</b>	<b>Occipital_Mid_L</b>		<b>11.75</b>
		-24	-88	-4	Occipital_Inf_L		9.70
		-9	-100	-16	Lingual_L		9.08
		-27	-85	-19	Cerebellum_Crus1_L		7.52

RA  
[Recall  
vs.  
D. ...]

<b>260</b>	<b>24</b>	<b>-94</b>	<b>8</b>	<b>Occipital_Mid_R</b>		<b>10.71</b>
	15	-94	-13	Lingual_R	17	6.4
	27	-79	-19	Cerebellum_6_R		7.35
	30	-79	-22	Cerebellum_Crus1_R		7.09
<b>21</b>	<b>-48</b>	<b>-4</b>	<b>53</b>	<b>Precentral_L</b>	<b>6</b>	<b>7.00</b>
<b>69</b>	<b>-63</b>	<b>-25</b>	<b>2</b>	<b>Temporal_Mid_L</b>	<b>22</b>	<b>6.66</b>
	-63	-22	5	Temporal_Sup_L		5.71
<b>66</b>	<b>60</b>	<b>-19</b>	<b>-1</b>	<b>Temporal_Sup_R</b>	<b>21</b>	<b>5.90</b>
	36	-31	-7	Hippocampus_R		3.52*
<b>43</b>	<b>51</b>	<b>14</b>	<b>-13</b>	<b>Temporal_Pole_Sup_R</b>		<b>5.45</b>
	42	20	-13	Frontal_Inf_Orb_R	47	5.03
<b>24</b>	<b>-57</b>	<b>8</b>	<b>17</b>	<b>Frontal_Inf_Oper_L</b>	<b>44</b>	<b>5.44</b>
	-51	17	23	Frontal_Inf_Tri_L		5.01
<b>13</b>	<b>-60</b>	<b>-37</b>	<b>17</b>	<b>Temporal_Sup_L</b>	<b>22</b>	<b>5.34</b>
<b>13</b>	<b>-48</b>	<b>-34</b>	<b>56</b>	<b>Postcentral_L</b>	<b>2</b>	<b>5.30</b>
	-39	-52	47	Parietal_Inf_L	40	4.71*

TABLE A.2: Activated regions for the contrast GE vs. Control. The number of voxels in the cluster (k), the x, y, and z coordinates in millimeters, the anatomical region according to AAL atlas (Tzourio-Mazoyer et al., 2002), the Brodmann Area (BA), and the T value are indicated for each peak. All activations were obtained at  $p < .05$  corrected except for those with asterisks in the table ( $*p < .001$  uncorrected). Abbreviation: GE = Sentence Generation.

Contrast	k	x (mm)	y (mm)	z (mm)	AAL	BA	T
GE [Sentence generation vs. control]	<b>383</b>	<b>-3</b>	<b>14</b>	<b>50</b>	<b>Supp_Motor_Area_L</b>	<b>6</b>	<b>10.21</b>
		3	14	50	Supp_Motor_Area_R	6	8.88
		-6	23	32	Cingulum_Mid_L		9.85
		15	20	35	Cingulum_Mid_R		7.21
		-9	17	44	Frontal_Sup_Medial_L		8.81
		-6	26	29	Cingulum_Ant_L		8
		12	26	23	Cingulum_Ant_R		7.1
		6	20	44	Frontal_Sup_Medial_R	32	7.45
		-12	14	47	Frontal_Sup_L		6.93
		-39	20	-7	Frontal_Inf_Orb_L		6.7*
		-51	8	-4	Temporal_Pole_Sup_L	38	4.64*
		<b>11</b>	<b>6</b>	<b>11</b>	<b>Cingulate_Ant_R</b>		<b>8.48</b>
		<b>16</b>	<b>48</b>	<b>-25</b>	<b>Temporal_Mid_R</b>		<b>8.17</b>
		<b>37</b>	<b>39</b>	<b>-55</b>	<b>Cerebelum_Crus1_R</b>		<b>8.14</b>
			33	-55	Cerebelum_6_R		7.36
		<b>43</b>	<b>-24</b>	<b>23</b>	<b>Insula_L</b>		<b>8.1</b>
		<b>15</b>	<b>-54</b>	<b>20</b>	<b>Frontal_Inf_Tri_L</b>	<b>45</b>	<b>7.55</b>
			-54	11	Frontal_Inf_Oper_L	44	6.59
		<b>17</b>	<b>6</b>	<b>-70</b>	<b>Vermis_6</b>		<b>7.14</b>
		<b>239</b>	<b>-51</b>	<b>-34</b>	<b>Temporal_Mid_L</b>	<b>21/22</b>	<b>6.07*</b>
		-48	-34	Temporal_Sup_L		3.59*	
	<b>31</b>	<b>30</b>	<b>-49</b>	<b>Precuneus_R</b>		<b>4.44*</b>	

TABLE A.3: Activated regions for the Encoding during sentence generation (GE task) obtained as a contrast between items that have later been correctly or incorrectly recognized (RECO task), modelled as an event-paradigm. The number of voxels in the cluster (k), the x, y, and z coordinates in millimeters, the anatomical region according to AAL atlas (Tzourio-Mazoyer et al., 2002), the Brodmann Area (BA), and the T value are indicated for each peak. All activations were obtained at  $p < .05$  corrected except for those with asterisks in the table ( $*p < .001$  uncorrected). Abbreviation: ENCO = Encoding during sentence generation.

Contrast	k	x (mm)	y (mm)	z (mm)	AAL	BA	T
ENCO [correct vs. incorrect]	<b>101</b>	<b>-51</b>	<b>20</b>	<b>-4</b>	<b>Frontal_Inf_Orb_2_L</b>		<b>10.20</b>
		-48	14	14	Frontal_Inf_Oper_L		9.19
		-48	29	2	Frontal_Inf_Tri_L		8.81
	<b>161</b>	<b>-42</b>	<b>-37</b>	<b>20</b>	<b>Temporal_Sup_L</b>		<b>9.84</b>
		-63	-28	2	Temporal_Mid_L		7.42
		-18	-13	-16	Hippocampus_L		4.27*
		-51	8	-10	Temporal_Pole_Sup_L		6.56
	<b>71</b>	<b>-3</b>	<b>5</b>	<b>68</b>	<b>Supp_Motor_Area_L</b>		<b>9.23</b>
	<b>105</b>	<b>39</b>	<b>-25</b>	<b>5</b>	<b>Heschl_R</b>		<b>8.56</b>
		51	-25	2	Temporal_Sup_R		7.5
		51	-22	-7	Temporal_Mid_R		6.72
	<b>24</b>	<b>33</b>	<b>-10</b>	<b>-22</b>	<b>Hippocampus_R</b>		<b>4.56*</b>
		21	-13	-19	ParaHippocampal_R		4.06

TABLE A.4: Activated regions for the contrast Correct vs. Incorrect during the RECO task. The number of voxels in the cluster (k), the x, y, and z coordinates in millimeters, the anatomical region according to AAL atlas (Tzourio-Mazoyer et al., 2002), the Brodmann Area (BA), and the T value are indicated for each peak. All activations were obtained at  $p < .05$  corrected except for those with asterisks in the table ( $*p < .001$  uncorrected). Abbreviation: RECO = recognition of items.

Contrast	k	x (mm)	y (mm)	z (mm)	AAL	BA	T
RECO [Correct vs. Incorrect]	<b>3356</b>	<b>-36</b>	<b>-82</b>	<b>-4</b>	<b>Occipital_Mid_L</b>		<b>17.07</b>
		18	-94	11	Cuneus_R		16.75
		42	-73	-10	Occipital_Inf_R		16.29
		-30	-52	-13	Fusiform_L		14.21
		36	-55	-16	Fusiform_R		12.5
		-42	-46	-16	Temporal_Inf_L	37	12.26
		-30	-61	-22	Cerebellum_6_L		12.17
		15	-85	-10	Lingual_R		11.7
		-24	-64	-10	Lingual_L		11.32
		48	-52	-16	Temporal_Inf_R	37	11.17
		27	-58	-22	Cerebellum_6_R		10.84
		-24	-46	-22	Cerebellum_4_5_L		10.69
		24	-46	-22	Cerebellum_4_5_R		9.77
		-42	-58	-4	Temporal_Mid_L		9.26
		-42	-67	-22	Cerebellum_Crus_1_L		8.41
		36	-22	-22	ParaHippocampal_R		5.25*
		-27	-28	-22	ParaHippocampal_L		6.05*
		-18	-61	32	Precuneus_L		5.44*
	<b>788</b>	<b>-39</b>	<b>-31</b>	<b>50</b>	<b>Postcentral_L</b>		<b>16.99</b>

	-39	-19	56	Precentral_L	3	15.31
	-39	-40	50	Parietal_Inf_L		10.67
	-24	-67	47	Parietal_Sup_L	7	10.67
	-54	-22	41	SupraMarginal_L		9.35
<b>154</b>	<b>-3</b>	<b>-4</b>	<b>53</b>	<b>Supp_Motor_Area_L</b>		<b>10.87</b>
	0	23	44	Frontal_Sup_Medial_L		8.56
	0	-4	50	Cingulum_Mid_L		8.34
	3	23	41	Frontal_Sup_Medial_R		7.5
<b>92</b>	<b>-45</b>	<b>11</b>	<b>32</b>	<b>Precentral_L</b>		<b>11.4</b>
	-48	14	32	Frontal_Inf_Oper_L		10.05
	-42	8	35	Frontal_Mid_L		8.88
	-42	14	26	Frontal_Inf_Tri_L		7.35
<b>61</b>	<b>-36</b>	<b>26</b>	<b>-1</b>	<b>Frontal_Inf_Tri_L</b>		<b>11.4</b>
	-30	26	-1	Insula_L		10.13
	-36	26	-4	Frontal_Inf_Orb_L		9.97
<b>57</b>	<b>-15</b>	<b>-25</b>	<b>-1</b>	<b>Thalamus_L</b>		<b>8.47</b>
	-15	-31	-4	Hippocampus_L		7.77
<b>29</b>	<b>24</b>	<b>-31</b>	<b>2</b>	<b>Hippocampus_R</b>		<b>8.79</b>
<b>17</b>	<b>-57</b>	<b>-16</b>	<b>20</b>	<b>Postcentral_L</b>		<b>8.56</b>
<b>15</b>	<b>0</b>	<b>2</b>	<b>26</b>	<b>Cingulate_Ant_L</b>		<b>9.47</b>

TABLE A.5: Activated regions for the contrast RECO\_OLD vs. RECO\_NEW and the opposite contrast. The number of voxels in the cluster (k), the x, y, and z coordinates in millimeters, the anatomical region according to AAL atlas (Tzourio-Mazoyer et al., 2002), the Brodmann Area (BA), and the T value are indicated for each peak. All activations were obtained at  $p < .05$  corrected except for those with asterisks in the table ( $*p < .001$  uncorrected). Abbreviation: RECO\_OLD = recognition of OLD items; RECO\_NEW = recognition of NEW items

Contrast	k	x (mm)	y (mm)	z (mm)	AAL	BA	T
	<b>210</b>	<b>-6</b>	<b>-67</b>	<b>35</b>	<b>Precuneus_L</b>	<b>7</b>	<b>10.59</b>
		-6	-64	26	Cuneus_L	31	9.91
RECO_OLD	<b>31</b>	<b>-45</b>	<b>-61</b>	<b>41</b>	<b>Angular_L</b>		<b>8.47</b>
vs.	<b>30</b>	<b>3</b>	<b>-25</b>	<b>35</b>	<b>Cingulate_Mid_R</b>	<b>24</b>	<b>8.10</b>
RECO_NEW		-6	-43	35	Cingulate_Mid_L	31	7.30
	<b>8</b>	<b>-45</b>	<b>-52</b>	<b>14</b>	<b>Temporal_Mid_L</b>		<b>7.91</b>
	<b>5</b>	<b>60</b>	<b>-49</b>	<b>8</b>	<b>Temporal_Mid_R</b>		<b>7.89</b>
	<b>168</b>	<b>27</b>	<b>-67</b>	<b>-7</b>	<b>Fusiform_R</b>		<b>6.47*</b>
		27	-52	-10	Lingual_R		4.33*
RECO_NEW	<b>143</b>	<b>-27</b>	<b>-85</b>	<b>-10</b>	<b>Occipital_Inf_L</b>		<b>6.19*</b>
vs.		-24	-88	-1	Occipital_Mid_L		5.48*
RECO_OLD		-27	-70	-7	Fusiform_L		4.87*
	<b>21</b>	<b>-27</b>	<b>-49</b>	<b>-16</b>	<b>Occipital_Mid_L</b>		<b>4.77*</b>
	<b>11</b>	<b>-33</b>	<b>-82</b>	<b>20</b>	<b>Occipital_Mid_R</b>		<b>4.69*</b>



TABLE A.6: Activated regions for the contrast RA vs. baseline. The number of voxels in the cluster (k), the x, y, and z coordinates in millimeters, the anatomical region according to AAL atlas (Tzourio-Mazoyer et al., 2002), the Brodmann Area (BA), and the T value are indicated for each peak. All activations were obtained at  $p < .05$  corrected except for those with asterisks in the table ( $*p < .001$  uncorrected). Abbreviation: RA = recall.

Contrast	k	x (mm)	y (mm)	z (mm)	AAL	BA	T
RA [Recall vs. Baseline]	<b>285</b>	<b>-45</b>	<b>8</b>	<b>23</b>	<b>Frontal_Inf_Oper_L</b>		<b>13.21</b>
		-45	18	17	Frontal_Inf_Tri_L		8.74
		-36	5	29	Precentral_L		6.89
		-41	8	35	Frontal_Mid_L		7.52
		-45	-37	14	Temporal_Sup_L		5.69*
		-42	14	-19	Temporal_Pole_Sup_L	38	5.55*
		<b>224</b>	<b>3</b>	<b>17</b>	<b>Supp_Motor_Area_R</b>	<b>8</b>	<b>11.61</b>
		-3	17	50	Supp_Motor_Area_L	8	10.32
		0	23	44	Frontal_Sup_Medial_L		10.74
		3	23	44	Frontal_Sup_Medial_R		10.44
		9	26	38	Cingulum_Mid_R	6	7.24
		-12	20	44	Frontal_Sup_L		5.17*
		<b>118</b>	<b>54</b>	<b>-28</b>	<b>Temporal_Sup_R</b>		<b>10.96</b>
		48	-22	-7	Temporal_Mid_R		6.74
		<b>71</b>	<b>27</b>	<b>-88</b>	<b>Occipital_Mid_R</b>		<b>10.72</b>
		27	-82	-16	Fusiform_R		7.31
		27	-88	5	Occipital_Mid_R		10.72
		30	-88	-5	Occipital_Inf_R	18	7.02
		15	-91	-7	Lingual_R		6.86
		24	-25	-7	Hippocampus_R		4.87*
		<b>45</b>	<b>36</b>	<b>26</b>	<b>Insula_R</b>		<b>9.09</b>
		33	26	-7	Frontal_Inf_Orb_R		7.52
		<b>108</b>	<b>-33</b>	<b>23</b>	<b>Insula_L</b>		<b>9.08</b>
		-42	26	-4	Frontal_Inf_Orb_L		9.07
		<b>92</b>	<b>-63</b>	<b>-31</b>	<b>Temporal_Mid_L</b>	<b>22</b>	<b>8.82</b>
		-63	-19	5	Temporal_Sup_L		6.68
		<b>68</b>	<b>-18</b>	<b>-94</b>	<b>Occipital_Mid_L</b>		<b>8.81</b>
		-21	-85	-13	Lingual_L		8.25
	-21	-82	-7	Fusiform_L		8.01	
	-21	-88	-4	Occipital_Inf_L		7.08	
	<b>16</b>	<b>9</b>	<b>-73</b>	<b>Cerebelum_Crus1_R</b>		<b>8.24</b>	
	<b>10</b>	<b>-33</b>	<b>-52</b>	<b>Parietal_Inf_L</b>		<b>8.21</b>	
	-33	-52	35	Angular_L		7.69*	

TABLE A.7: Activated regions for the paired t-test RA vs. GE. The number of voxels in the cluster (k), the x, y, and z coordinates in millimeters, the anatomical region according to AAL atlas (Tzourio-Mazoyer et al., 2002), the Brodmann Area (BA), and the T value are indicated for each peak. All activations were obtained at  $p < .05$  corrected except for those with asterisks in the table ( $*p < .001$  uncorrected). Abbreviation: RA = recall; GE = sentence Generation.

Contrast	k	x (mm)	y (mm)	z (mm)	AAL	BA	T
RA – GE [Recall vs. Sentence generation]	<b>21</b>	<b>-6</b>	<b>-67</b>	<b>32</b>	<b>Precuneus_L</b>	<b>7</b>	<b>7.98</b>
		3	-64	32	Precuneus_R	7	6.25*
		-6	-73	32	Cuneus_L		5.28*
		3	-76	35	Cuneus_R		3.64*
		<b>15</b>	<b>-27</b>	<b>-79</b>	<b>Fusiform_L</b>		<b>6.93</b>
		<b>25</b>	<b>27</b>	<b>-25</b>	<b>Hippocampus_R</b>		<b>3.93*</b>
			-33	-55	Parietal_Inf_L		6.12*
			-36	-55	Angular_L	40	5.32*
		<b>47</b>	<b>36</b>	<b>-70</b>	<b>Angular_R</b>		<b>4.85*</b>
		<b>21</b>	<b>-6</b>	<b>-40</b>	<b>Cingulate_Post_L</b>		<b>3.79*</b>

# Appendix B

## Chapter 3 Supplementary material

TABLE B.1: Demographic and clinical data for LTLE patients. Abbreviations: F – female; M – male; Age – age at the time of examination; Hand. – handedness evaluated with Edinburgh quotient (Oldfield, 1971); L – left, R – right; HA – hippocampal atrophy; Age onset – age of onset of seizures; AED – number of epileptic drugs taken; Seizure frequency: daily – seizures occurring on a daily basis, weekly – seizures occurring on a week basis, monthly – seizures occurring on a monthly basis; > monthly – seizures occurring once in couple of months.

	Demographic information				Clinical data			
	Sex	Age	Hand.	HA	Age onset	Epilepsy duration	AED	Seizure frequency
P1	M	28	R (+100%)	Yes	1	27	4	monthly
P2	M	45	R (+20%)	Yes	40	5	5	daily
P3	M	24	R (+100%)	Yes	17	7	3	weekly
P4	M	24	L (-80%)	Yes	16	8	3	monthly
P5	M	27	R (+80%)	No	20	7	3	daily
P6	F	26	R (+100%)	Yes	13	13	3	monthly
P7	F	43	R (+100%)	No	12	31	3	monthly
P8	F	43	R (+60%)	Yes	3	40	1	monthly
P9	F	38	R (+100%)	Yes	10	28	3	monthly
P10	M	24	R (+40%)	Yes	20	4	4	>monthly
P11	F	54	R (+90%)	No	52	2	2	weekly
P12	F	37	R (+100%)	No	35	2	2	>monthly
P13	M	24	R (+100%)	No	23	1	2	monthly
P14	F	32	R (+90%)	Yes	29	3	2	daily
P15	F	23	R (+100%)	Yes	8	15	2	weekly
P16	M	58	R (+90%)	No	14	44	2	monthly
P17	F	37	R (+90%)	Yes	36	1	5	daily
P18	F	41	R (+90%)	Yes	15	26	1	daily
Mean (SD)	10F/ 8M	34 (10.9)	17R/ 1L	12Y/ 5N	20.2 (13.5)	14.6 (14.2)	2.8 (1.2)	5D/3W/ 8M/2<M

TABLE B.2: Neuropsychological data for LTLE patients. Abbreviations: VCI – standardized score of verbal comprehension index for verbal semantic memory (Wechsler, 2008); DO80 - standardized score for French version of naming task (Deloche & Hannequin, 1997); SFL – semantic fluency, z core of performance on the task of categorical word generation (Godefroy & GREFEX, 2008), PFL – phonological fluency, z score of performance on the task of alphabetical word generation (Godefroy & GREFEX, 2008); AMI – standardized score of auditory memory (Wechsler, 2009); VMI – standardized score of visual memory (Wechsler, 2009); IMI - standardized score of immediate memory (Wechsler, 2009); DMI – standardized score for delayed memory (Wechsler, 2009).

	Language and memory scores							
	VCI	DO 80	SFL	PFL	AMI	VMI	IMI	DMI
P1	0.28	0.70	-0.24	-1.03	0.67	1.56	1.08	1.34
P2	-0.28	-1.30	-0.67	-1.28	-0.52	0	-0.08	-0.28
P3	/	-1.30	-0.34	-1.75	/	/	/	/
P4	-0.41	-2.20	-2.17	-0.97	-3.47	-0.61	-1.88	-2.33
P5	0.00	-0.03	-0.34	-0.34	1.34	-1.13	0.13	0.00
P6	-0.52	-2.05	-1.89	-1.52	0.28	0	-0.47	0.47
P7	0.28	-1.30	-1.46	-2.05	0.09	-1.75	-0.08	-1.13
P8	0.52	-0.3	-2.05	-2.05	-0.28	-0.2	-0.47	-0.28
P9	-1.56	-5.30	-0.98	-0.34	0.47	0	0.41	0.08
P10	-0.13	-4.30	1.66	-0.17	0.61	-0.2	0.47	-0.08
P11	0.00	0.67	1.39	-0.18	0.33	-1.08	-0.99	-0.28
P12	0.00	-0.30	0.34	-0.30	1.34	-2.05	-0.47	-0.74
P13	0.52	-1.3	0.64	0.68	0.08	-0.61	-0.28	-0.47
P14	-1.08	-1.46	-0.98	-0.34	-1.08	-1.18	-1.56	-1.41
P15	0.81	0.26	-0.34	-1.75	2.05	0.81	1.75	1.48
P16	1.08	-1.3	-1.28	-0.93	0.33	0.47	0.47	0.47
P17	-0.28	-0.17	-1.46	-2.05	-0.99	-1.6	-1.48	-1.65
P18	/	/	/	/	/	/	/	/
Mean (SD)	-0.05 (0.67)	-1.25 (1.62)	-0.6 (1.13)	-0.96 (0.82)	0.08 (1.25)	-0.47 (0.97)	-0.21 (0.97)	-0.30 (1.01)

TABLE B.3: Behavioral performance and differences between LTLE and HC during the RECO task. Abbreviations: %CR – percentage of correct responses; %ER – percentage of incorrect responses; %NR – Percentage of items without response; RT – reaction time in seconds; LTLE – left temporal lobe epilepsy; HC – healthy controls; The difference in performance between HC and LTLE patients is represented by values of Mann-Whitney U tests with the corresponding p-value.

	Old items				New items				All items				
	%CR	%ER	%NR	RT	%CR	%ER	%NR	RT	%CR	%ER	%NR	RT	
Mean	LTLE	72.4	21	6.67	1.08	75.6	13.8	10.7	1.18	74	17.4	8.68	1.13
	HC	71.2	24.9	3.82	0.97	87.5	4.61	8.03	1.12	79.3	14.7	5.91	1.05
Median	LTLE	73.8	20	6.25	1.08	81.3	7.5	7.5	1.2	75	16.3	8.13	1.12
	HC	72.5	25	5	0.96	87.5	2.5	7.5	1.13	81.3	13.8	6.25	1.05
SD	LTLE	8.81	8.45	4.93	0.1	17.4	14.5	10.8	0.11	8.24	7.31	6.87	0.08
	HC	9.55	9.98	2.41	0.08	7.36	5.42	6.1	0.07	6.54	5.83	3.72	0.05
Difference	U	152	126	110.5	74.5	96.5	88	158.5	85.5	105	118	134.5	39
	p	0.572	0.173	0.062	0.003	0.024	0.011	0.713	0.01	0.046	0.112	0.272	<.001

TABLE B.4: Activated regions for the contrast GE (generation with implicit encoding) vs. baseline. For each peak, the number of voxels in the cluster (k), T value, x, y, z coordinates (in mm), and region label (AAL atlas, Tzourio-Mazoyer et al., 2002) are presented. Activations were obtained at  $T_{GE} > 6.89$  ( $p < .05$ , FWE corrected). T values marked with \* were obtained at  $T_{GE} > 3.65$  ( $p < .001$ , uncorrected).

Contrast	k	T	x	y	z	AAL
GE vs. baseline	69	9.99	42	-60	-30	Cerebelum_Crus1_R
		7.97	33	-60	-27	Cerebelum_6_R
		7.74	18	-87	-6	Lingual_R
		6.67*	27	-93	12	Occipital_Mid_R
		7.65	21	-96	15	Occipital_Sup_R
		5.14*	24	-81	-15	Fusiform_R
	52	9.55	21	-96	9	Cuneus_R
		8.64	15	-93	0	Calcarine_R
		7.69	21	-93	6	Occipital_Sup_R
	34	9.36	-21	-93	3	Occipital_Mid_L
		7.71	-15	-90	-12	Lingual_L
	40	9.32	-3	12	60	Supp_Mot_Area_L
		6.76*	-54	-39	12	Temporal_Sup_L
	42	9.28	60	-15	-9	Temporal_Sup_R
		7.49	60	-12	-12	Temporal_Mid_R
	22	8.58	-54	18	18	Frontal_Inf_Tri_L
		8.24	-54	15	18	Frontal_Inf_Oper_L
		6.56*	-42	24	-6	Frontal_Inf_Orb_L
	8	8.28	-60	-18	-3	Temporal_Mid_L
	8	7.85	-39	15	21	Frontal_Inf_Tri_L
	5	7.46	-57	-39	3	Temporal_Mid_L
	7	7.42	-45	-60	-27	Cerebelum_Crus1_L
	68	5.9*	-15	-24	-18	Parahippocampal_L
	5.19*	-18	-24	-9	Hippocampus_L	

TABLE B.5: Activated regions for the contrast RECO (recognition) vs. baseline. For each peak, the number of voxels in the cluster (k), T value, x, y, z coordinates (in mm), and region label (AAL atlas, Tzourio-Mazoyer et al., 2002) and are presented. Activations were obtained at  $T_{RECO} > 7.03$  ( $p < .05$ , FWE corrected). T values marked with \* were obtained at  $T_{RECO} > 3.65$  ( $p < .001$ , uncorrected).

Contrast	k	T	x	y	z	AAL
RECO vs. baseline	828	20.26	33	-45	-18	Fusiform_R
		15.02	36	-81	-12	Occipital_Inf_R
		14.05	21	-93	0	Calcarine_R
		16.4	30	-48	-21	Cerebelum_6_R
		8.68	45	-57	-15	Temporal_Inf_R
		8.08	24	-81	-9	Lingual_R
	845	17.50	-30	-87	6	Occipital_Mid_L
		14.50	-15	-90	-9	Occipital_Mid_L
		12.51	-30	-81	-6	Occipital_Inf_L
		11.44	-36	-51	-21	Fusiform_L
		11.17	-42	-57	-24	Cerebelum_6_L
		10.39	-42	-48	-15	Temporal_Inf_L
		7.68	-30	-81	-15	Lingual_L

155	11.88	3	15	45	Supp_Motor_Area_L
	8.15	-3	6	57	Supp_Motor_Area_L
	7.81	-9	-3	54	Supp_Motor_Area_R
	8.5	-3	21	42	Frontal_Sup_Medial_L
	8.27	-6	12	42	Cingulate_Mid_L
	8.68	6	15	42	Cingulate_Mid_R
15	10.20	-21	-27	-3	Thalamus_L
	7.13	-18	-27	3	Thalamus_L
	7.23	-21	-27	-6	Hippocampus_L
176	9.54	-27	-51	39	Parietal_Inf_L
	9.52	-30	-9	60	Precentral_L
	8.50	-36	-36	39	Postcentral_L
	7.26	-27	-9	57	Frontal_Sup_2_L
11	8.50	-48	3	27	Precentral_L
8	8.23	0	0	72	Supp_Motor_Area_L
17	7.64	-24	-6	6	Putamen_L
6	7.55	-30	21	3	Insula_L
6	7.52	-45	18	21	Frontal_Inf_Tri_L
5	7.45	30	21	0	Putamen_R
84	6.55*	33	-3	-21	Amygdala_R
	5.71*	30	15	-21	Insula_R
	4.95*	24	-6	-21	Hippocampus_R
86	5.31*	30	-54	48	Parietal_Inf_R

TABLE B.6: Activated regions for the contrast RA (sentence recall) vs. baseline. For each peak, the number of voxels in the cluster (k), T value, x, y, z coordinates (in mm), and region label (AAL atlas, Tzourio-Mazoyer et al., 2002) and are presented. Activations were obtained at  $T_{RA} > 6.85$  ( $p < .05$ , FWE corrected). T values marked with \* were obtained at  $T_{RA} > 3.65$  ( $p < .001$ , uncorrected).

Contrast	k	T	x	y	z	AAL	
RA vs. baseline	113	10.51	3	30	42	Frontal_Sup_Medial_L	
		7.39	-3	15	51	Supp_Motor_Area_L	
		10.4	6	27	42	Frontal_Sup_Medial_R	
		9.24	2	24	4	Supp_Motor_Area_R	
		4.85*	-27	-33	-3	Hippocampus_L	
	102	10.50	-57	-21	0	Temporal_Mid_L	
		7.76	-54	-36	9	Temporal_Sup_L	
	64	9.14	60	-12	0	Temporal_Sup_R	
	85	4.68*	-30	-63	42	Parietal_Inf_L	
	43	8.85	30	-90	12	Occipital_Mid_R	
		8.15	27	-90	12	Occipital_Sup_R	
		23	8.57	-21	-96	3	Occipital_Mid_L
		34	8.32	-30	27	-3	Insula_L
			7.40	-42	21	-9	Frontal_Inf_Orb_2_L
	26	8.19	-48	18	24	Frontal_Inf_Tri_L	
		7.64	-51	15	21	Frontal_Inf_Oper_L	
5		7.96	-36	6	51	Frontal_Mid_2_L	

TABLE B.7: Percentage of the number of activated voxels in our regions of interest for language and memory included in the LMN. We generated maps for terms "language" and "memory" which yielded 1101 and 2744 studies respectively in the Neurosynth database. Those maps were binarized and added up. GE2REC LMN maps for HC and LTLE were obtained using second-level group analyses for each group for all three tasks. These maps were binarized (using as threshold  $p < 0.001$ , uncorrected and  $k > 5$ ) and added up. A less permissive threshold ( $p < 0.001$ , uncorrected and  $k > 5$ ) was used to binarize GE2REC activation given the limited number of participants compared to the number of meta-analyses and participants in Neurosynth. Each resulting image (Neurosynth LMN, LTLE LMN, and HC LMN) was projected on the AAL atlas. The percentage of activated voxels was calculated for each AAL region by dividing the number of activated voxels by the total number of voxels in a specific region. Regions including more than 30-50% activated voxels are yellow, 50-70% blue, and above 70% green. See also Figure 3.4.

Abbreviations: HC = Healthy controls; LTLE = Left temporal lobe epilepsy.

Lobe	region	Neurosynth	GE2REC HC	GE2REC LTLE
Frontal	Frontal_Inf_Oper_L	81.41	84.78	87.76
	Frontal_Inf_Oper_R	8.36	38.10	21.02
	Frontal_Inf_Orb_2_L	69.29	60.81	53.93
	Frontal_Inf_Orb_2_R	2.97	29.63	18.31
	Frontal_Inf_Tri_L	77.50	69.67	74.22
	Frontal_Inf_Tri_R	25.10	18.78	37.94
	Frontal_Med_Orb_L	0.28	0.00	0.00
	Frontal_Med_Orb_R	0.00	0.00	0.00
	Frontal_Mid_2_L	36.15	14.66	16.17
	Frontal_Mid_2_R	23.21	8.48	3.29
	Frontal_Sup_2_L	9.30	14.28	13.87
	Frontal_Sup_2_R	9.19	2.30	0.20
	Frontal_Sup_Medial_L	15.74	16.88	11.90
	Frontal_Sup_Medial_R	1.78	7.45	6.94
	OFCant_L	2.26	0.00	0.90
	OFCant_R	0.46	0.31	0.00
	OFClat_L	61.93	0.00	0.00
	OFClat_R	0.00	0.00	0.00
	OFCmed_L	0.18	0.36	0.00
	OFCmed_R	0.00	0.32	0.00
	OFCpost_L	7.94	19.58	22.40
	OFCpost_R	0.53	13.19	9.27
	Olfactory_L	0.00	14.64	0.00
	Olfactory_R	0.00	2.42	6.92
	Paracentral_Lobule_L	0.00	0.00	0.96
	Paracentral_Lobule_R	0.00	0.00	0.00
	Precentral_L	32.90	58.14	59.61
	Precentral_R	3.43	18.60	0.59
	Rectus_L	0.23	0.00	0.00
	Rectus_R	0.00	2.15	0.00
	Rolandic_Oper_L	4.65	22.42	18.08
	Rolandic_Oper_R	1.35	2.10	6.69
	Supp_Motor_Area_L	28.78	67.68	67.91
Supp_Motor_Area_R	1.56	47.20	32.60	
Insula and Cingulate	Cingulate_Ant_L	0.07	30.64	6.93



	Cingulate_Ant_R	0.00	22.85	3.58
	Cingulate_Mid_L	6.03	23.13	17.52
	Cingulate_Mid_R	3.72	25.51	17.34
	Cingulate_Post_L	54.00	7.13	0.00
	Cingulate_Post_R	9.25	3.88	0.00
	Insula_L	9.47	54.47	35.90
	Insula_R	3.39	38.59	19.60
Temporal	Amygdala_L	0.00	67.73	0.00
	Amygdala_R	0.00	41.53	32.66
	Fusiform_L	35.19	66.06	58.66
	Fusiform_R	17.24	60.72	56.16
	Heschl_L	15.56	27.56	34.22
	Heschl_R	3.61	0.80	30.92
	Hippocampus_L	84.23	56.55	12.77
	Hippocampus_R	83.62	35.41	14.69
	ParaHippocampal_L	65.54	19.84	4.29
	ParaHippocampal_R	61.66	15.55	7.86
	Temporal_Inf_L	19.03	13.16	10.69
	Temporal_Inf_R	3.65	13.24	11.02
	Temporal_Mid_L	55.56	35.63	28.45
	Temporal_Mid_R	12.25	21.46	9.53
	Temporal_Pole_Mid_L	8.74	2.65	0.00
	Temporal_Pole_Mid_R	11.71	6.23	1.43
	Temporal_Pole_Sup_L	31.05	34.55	19.92
	Temporal_Pole_Sup_R	16.67	22.42	11.43
	Temporal_Sup_L	55.57	67.20	56.18
	Temporal_Sup_R	33.78	35.12	42.02
Parietal	Angular_L	44.93	9.38	11.17
	Angular_R	20.66	13.24	4.85
	Parietal_Inf_L	36.09	52.19	53.09
	Parietal_Inf_R	24.01	7.81	7.43
	Parietal_Sup_L	18.74	37.87	21.65
	Parietal_Sup_R	4.32	13.46	2.75
	Postcentral_L	6.27	50.00	39.11
	Postcentral_R	1.44	15.38	0.92
	Precuneus_L	20.80	2.55	1.16
	Precuneus_R	22.11	2.17	0.25
	SupraMarginal_L	5.41	12.10	15.84
	SupraMarginal_R	3.50	3.09	0.30
Occipital	Calcarine_L	7.48	66.08	27.77
	Calcarine_R	4.51	77.92	35.36
	Cuneus_L	7.01	17.37	0.07
	Cuneus_R	3.51	21.70	8.92
	Lingual_L	5.68	80.33	38.81
	Lingual_R	7.91	80.74	32.57
	Occipital_Inf_L	16.58	71.52	62.17
	Occipital_Inf_R	1.01	42.37	37.51
	Occipital_Mid_L	14.65	50.49	51.74
	Occipital_Mid_R	8.67	41.85	33.41
	Occipital_Sup_L	2.42	44.07	27.38
	Occipital_Sup_R	4.74	48.48	16.49
Grey matter nuclei	Caudate_L	3.12	19.02	8.00
	Caudate_R	0.80	59.26	6.34

	Pallidum_L	1.37	76.79	79.52
	Pallidum_R	0.00	41.43	42.86
	Putamen_L	0.50	82.06	69.38
	Putamen_R	0.75	32.80	20.49
	Thalamus_L	0.91	79.64	52.55
	Thalamus_R	0.76	44.75	8.42
Cerebellum	Cerebelum_10_L	0.00	0.00	0.00
	Cerebelum_10_R	0.00	0.00	0.00
	Cerebelum_3_L	4.41	1.47	0.00
	Cerebelum_3_R	5.80	1.45	0.00
	Cerebelum_4_5_L	4.62	34.22	15.73
	Cerebelum_4_5_R	11.85	73.05	32.06
	Cerebelum_6_L	0.71	79.99	58.50
	Cerebelum_6_R	6.96	84.51	85.13
	Cerebelum_7b_L	0.00	4.27	0.00
	Cerebelum_7b_R	4.31	0.00	0.00
	Cerebelum_8_L	0.00	6.68	0.00
	Cerebelum_8_R	2.12	3.16	1.60
	Cerebelum_9_L	0.00	1.73	0.00
	Cerebelum_9_R	0.12	3.83	0.00
	Cerebelum_Crus1_L	2.07	27.24	25.12
	Cerebelum_Crus1_R	9.03	30.10	29.53
	Cerebelum_Crus2_L	0.05	5.86	2.27
	Cerebelum_Crus2_R	2.74	4.96	3.12
	Vermis_1_2	0.00	0.00	0.00
	Vermis_10	0.00	0.00	0.00
	Vermis_3	1.32	17.11	18.42
	Vermis_4_5	3.61	55.79	22.26
	Vermis_6	5.12	93.26	29.38
	Vermis_7	33.51	90.72	62.37
	Vermis_8	0.82	66.26	0.41
	Vermis_9	0.00	47.13	0.00

Since data did not meet the criteria for ANOVA (normality  $W = 0.879$ ,  $p < .001$ ), we performed Kruskal–Wallis tests for each lobe. The results showed that there was no significant difference in the general coverage of the frontal ( $\chi^2(2) = 0.682$ ,  $p = .711$ ), temporal ( $\chi^2(2) = 3.07$ ,  $p = .216$ ), and parietal lobe ( $\chi^2(2) = 1.94$ ,  $p = .379$ ) nor insula and cingulum ( $\chi^2(2) = 5.87$ ,  $p = .05$ ). Although by comparing the percentages directly, we can see that the mesial temporal regions were less activated than expected, especially in the LTLE group. Significant differences between the general lobe coverage were found for grey matter nuclei ( $\chi^2(2) = 16.2$ ,  $p < .001$ ; DSCF post-hoc showed higher coverage using GE2REC both in HC ( $W = 4.75$ ,  $p = .002$ ) and LTLE ( $W = 4.75$ ,  $p = .002$ ) than based on Neurosynth maps, while there was no difference between HC and LTLE ( $W = -1.93$ ,  $p = .359$ ), the occipital lobe ( $\chi^2(2) = 22.7$ ,  $p < .001$ , higher coverage using GE2REC both in HC ( $W = 5.88$ ,  $p < .001$ ) and LTLE ( $W = 4.65$ ,  $p = .003$ ) than based on Neurosynth maps, while the coverage was greater in HC than LTLE ( $W = -3.59$ ,  $p = .03$ ) and the cerebellum ( $\chi^2(2) = 7.57$ ,  $p = .023$ , higher coverage using GE2REC in HC ( $W = 3.756$ ,  $p = .022$ ) than based on Neurosynth maps, while there was no difference between Neurosynth and LTLE ( $W = 0.45$ ,  $p = .945$ ), nor between HC and LTLE ( $W = -2.845$ ,  $p = .109$ )).

TABLE B.8: Lateralization indices for GE2REC tasks in LTLE and HC. The number of participants in each group showing left, bilateral and right predominance for frontal, temporal, and hippocampus for each task are shown. Levene’s test results for the equality of variance and Mann-Whitney U for testing differences between LTLE and HC for each lobe/structure are also presented. Abbreviations: N = participant number; LTLE = Left temporal lobe epilepsy; HC = Healthy controls; L = left-lateralized; B = bilateral; R = right-lateralized; M = Mean; SD = standard deviation; Var diff = value of Levene’s test for the equality of variances with corresponding p-value; Diff = Values of Mann-Whitney U for testing differences between LTLE and HC with corresponding p-value.

	Sentence generation with encoding			Recognition of items			Recall		
	Frontal	Temporal	Hippocampus	Frontal	Temporal	Hippocampus	Frontal	Temporal	Hippocampus
LTLE	L 15 (83.3%)	14 (77.8%)	8 (44.4%)	13 (72.2%)	6 (33.3%)	5 (27.8%)	13 (72.2%)	16 (88.9%)	10 (55.6%)
	B 1 (5.6%)	4 (22.2%)	3 (16.7%)	3 (16.7%)	6 (33.3%)	3 (16.7%)	3 (16.7%)	1 (5.6%)	3 (16.7%)
	R 2 (11.1%)	0 (0%)	7 (38.9%)	2 (11.1%)	6 (33.3%)	10 (55.6%)	2 (11.1%)	1 (5.6%)	5 (27.8%)
HC	L 17 (89.5%)	14 (73.7%)	15 (78.9%)	19 (100%)	7 (36.8%)	8 (42.1%)	17 (89.5%)	12 (63.2%)	8 (42.1%)
	B 2 (10.5%)	5 (26.3%)	2 (10.5%)	0 (0%)	10 (52.6%)	7 (36.8%)	2 (10.5%)	5 (26.3%)	5 (26.3%)
	R 0 (0%)	0 (0%)	2 (10.5%)	0 (0%)	2 (10.5%)	4 (21.1%)	0 (0%)	2 (10.5%)	6 (31.6%)
M	LTLE 0.56	0.46	0.02	0.42	-0.01	-0.15	0.42	0.38	0.24
	HC 0.62	0.47	0.37	0.59	0.11	0.09	0.55	0.36	0.05
SD	LTLE 0.462	0.273	0.664	0.385	0.326	0.45	0.11	0.332	0.139
	HC 0.231	0.289	0.358	0.131	0.265	0.367	0.05	0.339	0.14
Var diff.	3.98	0.04	12.69	16.45	1.85	1.356	7.36	1.05	0.003
p	0.054	0.842	<.001*	<.001*	0.183	0.252	0.01*	0.310	0.953
Diff	145	167	124	138	135	112	167	163	139
p	0.438	0.903	0.158	0.323	0.274	0.073	0.903	0.808	0.331

TABLE B.9: Activation differences between healthy and patients during GE (generation with implicit encoding). For each peak, the number of voxels in the cluster (k), T value, x, y, z coordinates (in mm), and region label (AAL atlas, Tzourio-Mazoyer et al., 2002) are presented. All activations were obtained at  $T > 3.35$  ( $p < .001$ , uncorrected).

Contrast	k	T	x	y	z	AAL
HC >LTLE	155	5.05	-15	-12	48	Cingulate_Mid_L
		4.59	-6	12	51	Supp_Motor_Area_L
		4.43	12	12	57	Supp_Motor_Area_R
	80	4.95	-21	-54	45	Parietal_Sup_L
		3.51	-27	-51	48	Parietal_Inf_L
	156	4.81	45	-18	45	Precentral_R
		4.37	45	-36	48	Parietal_Inf_R
		4.11	42	-27	54	Postcentral_R
	84	4.51	27	45	21	Frontal_Sup_2_R
		4.12	33	36	24	Frontal_Mid_2_R
	9	4.48	-9	-21	0	Thalamus_L
	29	4.47	48	0	30	Precentral_R
	50	4.32	54	12	3	Frontal_Inf_Oper_R
	27	4.25	6	6	0	Caudate_R
	10	4.12	-36	12	30	Frontal_Inf_Oper_L
	23	4.08	-48	9	0	Frontal_Inf_Oper_L
	20	4.06	-9	18	30	Cingulate_Ant_L
	5	4.04	6	-30	66	Paracentral_Lobule_R
	12	3.93	-15	12	-3	Putamen_L
	18	3.84	-48	-33	6	Temporal_Sup_L
	19	3.73	-45	0	45	Precentral_L
		3.72	-36	-3	42	Precentral_L
	7	3.71	-12	-42	51	Cingulate_Mid_L
	6	3.69	9	-24	51	Supp_Motor_Area_R
	25	3.65	24	-57	42	Angular_R
		3.50	12	-66	42	Precuneus_R
	6	3.57	-33	18	-3	Insula_L
	7	3.54	-45	-18	42	Postcentral_L
LTLE >HC	No suprathreshold clusters					

TABLE B.10: Activation differences between healthy and patients during RECO (recognition). For each peak, the number of voxels in the cluster (k), T value, x, y, z coordinates (in mm), and region label (AAL atlas, Tzourio-Mazoyer et al., 2002) are presented. All activations were obtained at  $T > 3.35$  ( $p < .001$ , uncorrected).

Contrast	k	T	x	y	z	AAL
HC >LTLE	63	5.07	-33	-36	45	Postcentral_L
		3.76	-27	-45	42	Parietal_Inf_L
	70	4.58	27	-54	-12	Fusiform_R
		3.77	21	-45	-15	Fusiform_R
		3.60	45	-48	0	Temporal_Mid_R
	12	4.25	24	-84	-9	Lingual_R
	10	3.89	-45	-21	24	Rolandic_Oper_L
	12	3.89	27	-72	51	Parietal_Sup_R
	8	3.88	-33	-18	57	Precentral_L
	12	3.86	-33	-75	15	Occipital_Mid_L

	3.61	-24	-84	15	Occipital_Mid_L
15	3.86	-24	-63	-9	Lingual_L
	3.76	-27	-60	-9	Fusiform_L
8	3.69	-39	-75	-3	Occipital_Mid_L
	3.63	-33	-84	-3	Occipital_Mid_L
5	3.67	0	3	30	Cingulate_Ant_L
11	3.64	45	-54	-15	Temporal_Inf_R
8	3.57	36	-75	0	Occipital_Mid_R
LTLE >HC		No suprathreshold clusters			

TABLE B.11: Activation differences between healthy and patients during RA (sentence recall). For each peak, the number of voxels in the cluster (k), T value, x, y, z coordinates (in mm), and region label (AAL atlas, Tzourio-Mazoyer et al., 2002) are presented. Activations were obtained at  $T > 3.35$  ( $p < .001$ , uncorrected).

Contrast	k	T	x	y	z	AAL
	19	4.40	51	15	3	Frontal_Inf_Oper_R
	13	4.08	39	12	-9	Insula_R
HC >LTLE	21	3.82	0	15	51	Supp_Motor_Area_L
		3.43	6	15	54	Supp_Motor_Area_R
	11	3.73	36	24	0	Insula_R
LTLE >HC		No suprathreshold clusters				

## B.1 Methodological issues of LI calculation

One of the major characteristics of brain functional organization is asymmetric processing of information or hemispheric lateralization (Seghier, 2008). The increasingly accessible fMRI method can provide results consistent with invasive methods such as the Wada test and electrical cortical stimulation, without the invasiveness (Bauer et al., 2014; Dym et al., 2011). Nevertheless, there is no conclusive agreement on the way this hemispheric lateralization should be measured or expressed when relying on fMRI data. In the present manuscript, we will briefly present different methods and techniques that can be found in the literature for accessing the hemispheric lateralization.

### B.1.1 The basic formula

Generally, the hemispheric dominance is expressed as the laterality index (LI), sometimes also referred to as asymmetry index. This index denotes the differences between left (LH) and right hemisphere (RH) in task-related activity and it is expressed as the relative difference between the involvement of LH and RH (Seghier, 2019). The classical LI formula is:

$$LI = \frac{Q_{LH} - Q_{RH}}{Q_{LH} + Q_{RH}}$$

Where Q refers to the quantity of LH and RH activity that are measured by fMRI. The positive values suggest LH dominance and negative values reflect RH dominance (Seghier, 2008). However, there are different approaches regarding the measurements taken as the “quantity of the activity”.

## B.1.2 Measurements used

Two main choices of the LH and RH activity measurement are signal extent and signal magnitude.

**Signal extent** refers to the absolute number of voxels that shows activity over certain threshold in each hemisphere. However, when using this measure, it is overlooked if the activation of the voxels is statistically higher in one hemisphere or the other, and that way the intensity of the differences is neglected (Bradshaw, Bishop, et al., 2017). **Signal magnitude** represents the average intensity of voxels over certain threshold in each hemisphere or magnitude of fMRI signal change. This can be expressed via weighted  $\beta$  value or the t values (Jansen et al., 2006)<sup>1</sup>.

Although for both measures yielded similar LI and curves (Wilke & Lidzba, 2007), there is also evidence that signal magnitude has higher reproducibility (Bradshaw, Bishop, et al., 2017; Jansen et al., 2006) and it is less affected by noise (Adcock et al., 2003), which is due to the fact that no threshold should be selected in order to calculate it (Bradshaw, Bishop, et al., 2017).

The issue with choosing signal magnitude as a measurement of hemispheric activity is that it is highly dependent on the choice of ROI. At the same time, selected ROIs should be small because if large ROIs (such as the whole hemisphere) are compared, there is a risk that the main activation centers in LR and RH might not be the same, so the areas that are being compared are not homologous (Jansen et al., 2006). Additionally, the underlying assumption is that what is being analyzed are the activations. However, ROI can also be "deactivated" if the activation during the control is higher than the one during the task. A solution that has been proposed is to only compare BOLD intensity in those voxels that are most strongly activated within each ROI. This approach can reproducibly determine hemispheric dominance and degree of lateralization (Jansen et al., 2006). If a study is interested in hemispheric dominance and the degree of lateralization within big ROIs (for example, the whole hemisphere), it is advised to base LIs on active voxel counts at variable thresholds (Jansen et al., 2006). The LH and RH activity quantity was also expressed through the average of correlation coefficients, weighted t values, mean signal change, and statistical F values. The problem with these measurements is that they can lead to negative values of QLH/QRH, which can result in misinterpretation of the obtained LI. Also, the contribution of these measures over the classically used ones has not been found (Chlebus et al., 2007; Seghier, 2008).

## B.1.3 The existing methods

The next important point is the method used to access LI. At the beginning of this overview, we have shown the classical LI ratio because it captures the general idea of hemispheric domination and is still the most widely used method (Bradshaw, Bishop, et al., 2017). However, the classical LI faces several issues, including overlooking the high inter-individual variability of signal strength and poor data quality (Suarez et

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<sup>1</sup> $\beta$  should be preferred when it is expected that the variance between the sessions changes (for example, when a lot of time has passed between the sessions or when the machine has been changed).

al., 2009). Nevertheless, the biggest challenge that the classical LI ratio is facing is threshold dependence.

### Thresholding

The majority of studies from 2000 used a *single fixed threshold* across subjects. Although widely used, this method faces several issues. First of all, the voxels that appear active at low thresholds can be falsely positive, leading to results suggesting bilaterality. Secondly, if, by wanting to avoid false bilaterality, a study adopts a high threshold, the number of activated voxels will decrease. There will be false positives among the lost voxels and genuinely activated ones, which can lead to more extreme values closer to  $\pm 1$ . Considering that it was shown that the change of statistical threshold could reverse the sign of LI, it is not advisable to use a single statistical threshold to evaluate hemispheric dominance (Bradshaw, Bishop, et al., 2017; Jansen et al., 2006).

One proposed solution to the thresholding problem was to show tendencies towards a pattern of dominance by calculating LI for multiple thresholds and producing a plot showing the change of LI as a function of a threshold. The idea was that since the *LI* curve reaches a plateau for a range of thresholds, for that part of the curve, we can vary the statistical threshold without observing the changes in the LI. Therefore, calculating the LI within this plateau makes the LI less dependent on the p-value. Nevertheless, this plateau is not always found, nor is it always possible to reproduce it (Bradshaw, Bishop, et al., 2017; Jansen et al., 2006).

Another group of solutions is to employ a *variable threshold*. In this method, the threshold is set for specific parameters of subjects, such as a fixed number of active voxels (Jansen et al., 2006). Despite the evidence that variable thresholds increase the reliability of activations and reproducibility of LI in comparison to a single fixed threshold (Fesl et al., 2010), this method still requires a decision on the number of voxels (Bradshaw, Bishop, et al., 2017). Moreover, different tasks may demand different threshold levels, and in subjects with a low activation level, this method can lead to higher type I errors (Jansen et al., 2006). Another variant of this method is to decide on the threshold as a proportion to the maximum or mean intensity of voxels (Bradshaw, Bishop, et al., 2017; Jansen et al., 2006). It has been shown that if only the voxels that form a significant cluster or that have a low level of variability are taken into calculation, LI tends to become more stable at different thresholds (Wilke & Lidzba, 2007).

### Threshold independent methods

There is a group of methods whose goal is to provide LI independent from the thresholding. One of the most used methods from this group is *t-weighting* (Branco et al., 2006). When applying this method, the distribution of voxels across all T values is multiplied by a weighting function so that higher thresholds are given greater weight. That way, the distribution is weighted by its statistical significance, and these values are then entered in the standard LI equation. This method applies to most fMRI designs yielding unambiguous lateralization, stable across different weighting functions, and congruent with Wada results (Suarez et al., 2009). Another threshold-independent

method was proposed by Nagata et al. (2001), in which the regression between the number of activated voxels and the threshold (z-score) was used as QLH/RH terms. The problem with the method proposed by Nagata et al. (2001) is that QLH/RH can have different relationships with the threshold in certain data sets and that it is necessary to use the same statistical interval for regression to compare lateralization between groups or tasks since the regression function can depend on the interval used for curve fitting (Seghier, 2008). Additionally, it is not theoretically based, and it did not receive much support in the literature (Jansen et al., 2006; Nagata et al., 2001).

### The flip method

One information that the classical LI method is not providing is the statistical significance of the hemispheric difference. The idea of The Flip method (Baciu et al., 2005) is to provide a comparison between the activation of the two hemispheres and to say how statistically significant is the divergence of their activations. This method consists of contrasting the right image set and the flip image. The first refers to the original function images for the contrast of interest, while the latter refers to its mirror image. The significant voxels that are identified through this contrast are then inserted in the classical LI equation. Although providing statistical significance, this method has received two main critiques (Bradshaw, Bishop, et al., 2017). First, it cannot be used to describe bilaterality. Secondly, this method yields a strong LI (close to  $-/+ 1$ ) preventing it, thus providing information on the degree of lateralization.

### Bootstrapping

Within this method proposed by Wilke and Schmithorst (2006), all voxel values for each hemisphere/ROI and for each threshold are taken from an image as a vector, and then multiple random samples from these vectors are created. The lateralization indices are calculated iteratively for all possible left-right sample combinations. Subsequently, a histogram of all these LIs is plotted, and a mean is calculated by taking only the central 50% of the data, which is done to reduce the effect of outliers. Finally, a weighted overall mean is calculated from this data by giving a higher weight to higher thresholds and the minimum and maximum LI, which gives a confidence interval for a given index. The main advantage of this approach is that it is threshold-independent, robust, resistant to outliers while also detecting the presence of the outliers. Moreover, the practical aspect of this approach is that it is provided as the SPM toolbox (Wilke & Lidzba, 2007). All of which accounts for wide usage of this method in recent years (for a review of studies using this method, see Bradshaw, Bishop, et al., 2017). Nevertheless, this method is still critically dependent on data pre-selection since the poor data quality can be reflected in LI values that indicate bilaterality (Wegrzyn et al., 2019).

#### B.1.4 Global LI or ROI LI?

Another critical issue when exploring hemispheric dominance is whether global LI (activation of the whole hemisphere) or LI of specific regions of interest (ROI) should be taken into account. Although global LI was found to be more reliable than regional LI in voxel count (Jansen et al., 2006), there are specific issues with the global LI that



advocate for ROI LI. First, in the case of the global LI, voxels outside the relevant language areas can influence the computation of the LI (Bradshaw, Bishop, et al., 2017). Additionally, crossed dominance (for instance, LH dominance for frontal regions and RH for temporal) or regional heterogeneity, which can be overseen if only global LI is used, provide a strong argument for using the ROI LI (Bradshaw, Bishop, et al., 2017; Seghier, 2008). Furthermore, there is a question of how to define an ROI. Generally, analyses can base on anatomically or functionally defined ROIs (Jansen et al., 2006). The problem with anatomically defined ROIs is that the task does not necessarily activate them, or the activations may lie outside the anatomically chosen regions. While the issue with the functionally defined ROIs is that they can include areas out of the areas of interest. Therefore, the authors are employing a combination of the two ROIs (Adcock et al., 2003; Jansen et al., 2006). General recommendations are that the ROIs should be chosen based on the studied language function or the purpose of the laterality measurement (Bradshaw, Bishop, et al., 2017). It is also advisable to use both regional and global ROIs for LI assessment for each subject to get the complete picture of language laterality (Seghier, 2008). Finally, it is suggested to consider multiple ROIs to improve the classification of the dominance (Benjamin et al., 2017; Wegrzyn et al., 2019).

### B.1.5 Classification of the hemispheric dominance

The LI scores are often used to decide the hemispheric dominance, especially in the clinical setting as a part of the presurgical evaluation (Bauer et al., 2014; Dym et al., 2011; Szafarski et al., 2017). The standard threshold for hemispheric dominance is 0.2, with values between -0.2 and 0.2 interpreted as bilaterality. It is important to note that these cut-off values have been taken irrespectively of the method used to calculate the IL (Seghier, 2019). There are also more nuanced categorizations making the distinction between strong or weak lateralization and bilateral representation. Indeed, the number of dominance categories depends on the brain function of interest (Seghier, 2019).

Another approach to categorize the dominance is to employ a variable and adapted LI threshold that is data-driven. That way, the threshold can be decided based on the group mean and SD of individual LI values or by comparing the LI distribution of a patient with the LI distribution of the control group. The latter approach is especially appropriate for comparing patients with the control subjects, but only in the case of highly lateralizing tasks with low variability in healthy subjects (Bradshaw, Bishop, et al., 2017). The authors also used the hierarchical clustering method, concluding on the cut-off based on the optimal cluster solution (Berl et al., 2014) or Gaussian mixture modeling (Mazoyer et al., 2014) to find dominance categories on laterality data in left and right-handed groups separately.

A recent study has confirmed that the cut-off of 0.2 is indeed an objective cut-off score for hemispheric dominance categorization (Seghier, 2019). And it was suggested that in the case of five dominance categories, studies should use 0.11 and 0.43 as cut-off scores. More importantly, this study proposed the objective cut-offs based on the statistical properties of the LI distribution. This is applicable when testing a cognitive function without prior knowledge of the size of actual lateralization bias. In that case,

the new LI formula should be used ( $LI = (LH - RH) / \max(LH, RH)$ ), which guarantees proper distance metrics. With the proposed formula, the three dominance categories can be made with cut-offs at  $\pm 1/3$  (Seghier, 2019).

Another important issue of hemispheric dominance classification that has already been mentioned while reviewing the existing methods is the bilateral laterality. Namely, it was shown that independently of chosen ROI and activity measures, subjects cannot reproducibly be categorized as bilateral (Jansen et al., 2006). The recommendation is to classify a subject as “bilateral” only after using various methods of calculation. In the case of “unstable” activation tasks for which activations can be found on the group levels, but only at a permissive threshold for certain subjects on an individual level, the advice is to adopt a “criterion of stability”, and hemispheric dominance should be evaluated only if a subject has sufficient activity at a typical statistical threshold (Jansen et al., 2006). This is also related to the already mentioned problem with different LI methods of not being sensitive to data quality. In other words, the mentioned methods cannot categorize data as inconclusive, and it is a decision only a trained specialist could make. Namely, Wegrzyn et al. (2019) have empirically demonstrated how a participant with a low number of activated voxels in both hemispheres can be classified either as bilateral or strongly right-lateralized by using adaptive threshold or fixed-threshold methods, respectively. These authors propose deconstructing the LI equation and using the information about the strength of overall activity ( $QLH + QRH$ ) to classify the case as inconclusive. Importantly, they have shown that using both  $QLH - QRH$  and  $QLH + QRH$  separately does not allow for better classification and that common LI (fixed threshold, adaptive threshold and bootstrap) is a helpful method for data reduction. However, their method allows for recognizing the inconclusive cases since they will be situated on the low point of the  $QLH - QRH$  scale and the low point of the  $QLH + QRH$  scale, which we cannot predict with fixed threshold, adaptive threshold, and bootstrap. Additionally, these authors have shown that no method could predict the inconclusive cases above the chance level. They took it as the argument to include this class when classifying to avoid misclassifications, especially in the clinical context. They advise alternative data analysis techniques in inconclusive data, such as pattern analysis methods (Zago et al., 2017).

Finally, another important aspect that should be considered when exploring hemispheric dominance: the task. Namely, different language tasks can yield within-subject dissociations in hemispheric dominance (Bradshaw, Bishop, et al., 2017). Moreover, different memory processes and types of stimuli can also result in different memory lateralization (Andreau & Torres Batán, 2019; Golby et al., 2002; Milian et al., 2015; Palacio & Cardenas, 2019). Nevertheless, this overview mainly focused on the approaches and issues when calculating LI from fMRI data. Recent studies also propose using resting fMRI as an alternative for task-based lateralization assessment (K. A. Smitha et al., 2019), which yielded promising results.

# Appendix C

## Chapter 4 Supplementary material

### C.1 Additional information on the Methods

#### C.1.1 Community detection algorithm – group level

Data-driven community structure was assessed by applying a modularity maximization algorithm (Louvain greedy algorithm, Blondel et al., 2008; Rubinov & Sporns, 2010) to previously described correlation matrices of individual participants with positive, weighted edges. Notably, the community partition can vary with each run of the algorithm (Rubinov & Sporns, 2010). In order to address the possibility of partition degeneracy, we applied the consensus approach (Lancichinetti & Fortunato, 2012; Sporns & Betzel, 2016) similarly implemented in prior studies (Dwyer et al., 2014; Hearne et al., 2017; Schedlbauer & Ekstrom, 2019). Additionally, the applied approach was meant to estimate the most stable network partitions across algorithm iterations and the thresholds proposed by Schedlbauer and Ekstrom (2019). It was suggested that partitions obtained in this way converge into one consensus partition (Sporns & Betzel, 2016). The procedure was performed for the resting-state and sentence recall task separately. Throughout the procedure, we used the Louvain greedy algorithm (Kruschwitz et al., 2015; Rubinov & Sporns, 2010) with the resolution parameter gamma of 1. For each subject, on each threshold (0.01 – 0.99 with 0.001 step) we calculated module partition 100 times because each iteration can give a slightly different outcome. These 100 repetitions partitions per subject were then used to calculate the agreement matrix on each threshold which shows how many times the two given nodes were assigned to the same module. This agreement matrix was then used to perform independent module partitioning ( $\tau = 0.5$ , 100 repetitions), which provided a module partition for each subject on each threshold. We took individual module partitions on each threshold and calculated the agreement matrix on which we again performed independent module partitioning ( $\tau = 0.5$ , 100 repetitions) in order to obtain module partition on a group level. Then, we took group module partitions for all thresholds and calculated the agreement matrix for them. Using this matrix, we executed module partitioning ( $\tau = 0.5$ , 100 repetitions) which gave us the final solution for which the modularity index  $Q$  was calculated (Rubinov & Sporns, 2010). Finally, due to the near-degeneracy of the Louvain algorithm, we performed optimization by repeating this procedure 100 times. For each pair of partitions Rand coefficient was calculated (Doron et al., 2012).

Then we looked for a partition with the highest average Rand coefficient compared to the other partitions, meaning that it was the partition that was the most similar to all others (Cole et al., 2014; Doron et al., 2012). We took as the final representative group partition the one with the highest average Rand coefficient. The group-level community structure detection was performed to obtain the most stable network partitions on a group level.

### C.1.2 Community detection algorithm – individual level

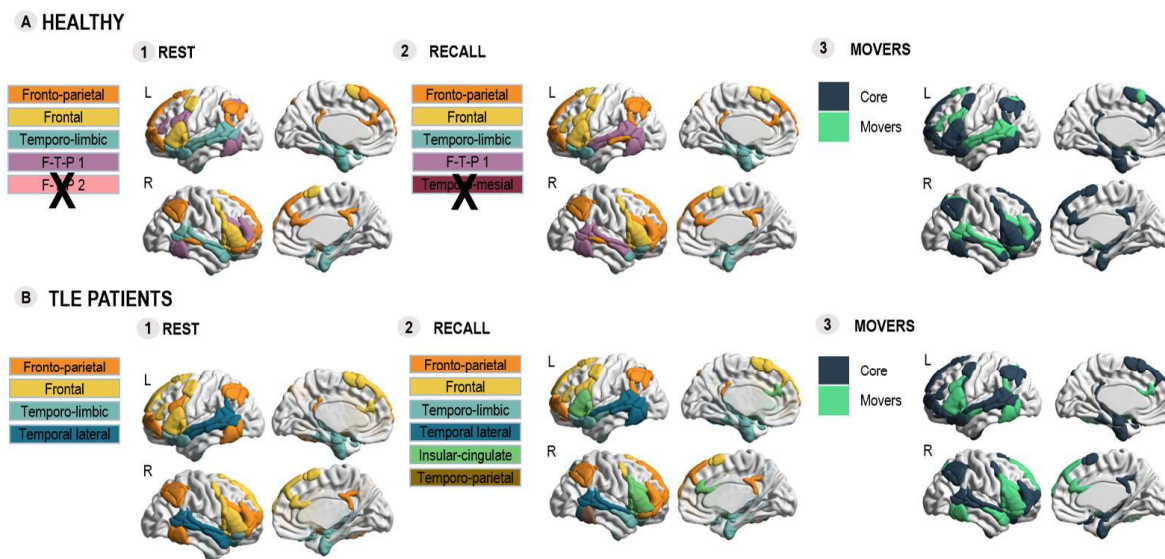
In the individual-level community structure detection, we applied a similar approach as in the group-level, only the optimization step was performed on the individual level and not the group. For each subject, on each threshold (0.01 – 0.99 with 0.001 step) we calculated module partition 100 times. These 100 repetitions partitions per subject were then used to calculate the agreement matrix on each threshold. This agreement matrix was then used to perform independent module partitioning ( $\tau = 0.5$ , 100 repetitions) which provided a module partition for each subject on each threshold. For each subject separately, we took module partitions for all thresholds and calculated the agreement matrix. Using this matrix, final module partitioning ( $\tau = 0.5$ , 100 repetitions) for which the modularity index  $Q$  was calculated (Rubinov & Sporns, 2010). Finally, 100 optimization repetitions for each subject were performed, yielding 100 final possible partitions. For each subject, the Rand coefficient was calculated for each pair of partitions, and we took as the final representative individual partition the one with the highest average Rand coefficient. These individual-level partitions were calculated to test the effectiveness of LMN configurations by relating them to clinical and neuropsychological characteristics of TLE patients.

### C.1.3 Repeated measure permutation procedure for VIn significance testing

To test if the module partitions vary between the tasks within a group and between two groups for each task, we used the variation of information (VIn). VIn quantifies the information intrinsic to the two partitions corrected by the information that they share (Meilă, 2007). To test the statistical significance of the obtained VIn, we implemented a repeated measure permutation procedure (Dwyer et al., 2014; Hearne et al., 2017). Namely, the condition labels for the partitions used as the input in the last run of module partition were randomly shuffled, creating the two new sets of module structures. Then the module partitions were obtained for these two new sets using the same procedure previously described. After that, the difference between these two new partitions was quantified via VIn. This process was repeated  $10^5$  times to obtain the null distributions of VIn for each contrast under the null hypothesis of random labeling of datasets. Finally, the actual VIn value for the contrast of interest was compared with this null distribution to generate its p-value.

### C.1.4 Community detection using positive and negative

We repeated our community detection analysis using both positive and negative correlations. The results are presented in Figure S1. The modules remained similar to the ones found using only positive correlations in both healthy participants and TLE patients (Figure 4.4 in the Main document). One important change is that there was no segregation of temporo-mesial module in healthy participants during recall task. This is not surprising considering the change of meaning of modules when also using negative correlations. Namely, we defined modules in our main study as densely intra-connected regions that share common functions that are sparsely connected with other communities (Fornito et al., 2016; Guimerà & Amaral, 2005; Rubinov & Sporns, 2010). Whereas, with signed networks the communities are group of regions that are internally positively correlated but externally anticorrelated (Sporns & Betzel, 2016). If it had segregated, it would mean that temporo-mesial module is negatively correlated with the other modules and that it has opposite goals or competing representations to other modules (Fox et al., 2005). Since this did not happen, it would mean that these regions indeed have a cooperative function and that they are most strongly cooperating with other regions engaged in declarative memory processes (both episodic and semantic) such as temporal pole, frontal inferior orbitalis and parahippocampus. We can explain in similar manner the fact that FTP2 did not segregate during resting-state, but it divided into other modules.



**Figure C.1:** Segregation of LMN in terms of community structures found in healthy participants (A) and TLE patients (B) during the two states using both positive and negative correlations. The architectures of modules are presented in the templates (Subpanels 1 and 2). Subpanels 3 shows the “core” regions of healthy participants and TLE patients that remain in the same module from rest to task (dark blue) and “movers” that change their module (light green). F-T-P = Fronto-temporo-parietal module, RECALL = sentence recall task, REST = resting-state. The X sign shows the modules found using only positive correlations that were not found when using both positive and negative correlations.

## C.2 Tables and additional analyzes

TABLE C.1: Demographic and clinical data for healthy controls. Abbreviations: F – female; M – male; Age – the age at the time of examination; Hand. – self-reported handedness; R – right; EZ lat. – laterality of epileptogenic zone; Vol hippo R – the volume of the right hippocampus in cm<sup>3</sup>; Vol hippo L – the volume of the left hippocampus in cm<sup>3</sup>.

	Demographic information			Clinical data	
	Gender	Age	Handedness	Vol hippo R	Vol hippo L
1	F	19	R	3.38	3.19
2	M	19	R	3.61	3.42
3	F	19	R	3.45	3.52

4	M	21	R	3.78	3.53
5	F	18	R	3.56	3.5
6	F	18	R	3.59	3.8
7	M	20	R	3.8	3.66
8	M	23	R	3.99	3.93
9	M	23	R	4.46	3.92
10	F	19	R	3.67	3.47
11	F	18	R	3.84	3.93
12	F	29	R	3.9	3.79
13	M	21	R	4.82	4.64
14	F	25	R	3.55	3.63
15	M	19	R	3.64	3.59
16	M	21	R	4.44	4.44
17	M	23	R	3.74	3.9
18	M	25	R	4.22	4.28
19	M	23	R	4.54	4.14
Mean	8F/ (SD)	21 (2.97)	19R	3.89 (0.41)	3.80 (0.37)

TABLE C.2: Demographic and clinical data for TLE patients. Abbreviations: F – female; M – male; Age – the age at the time of examination; Hand. – handedness evaluated with Edinburgh quotient (Oldfield, 1971); L – left, R – right; EZ lat. – laterality of epileptogenic zone; HA – hippocampal atrophy; Vol hippo R – the volume of the right hippocampus in cm<sup>3</sup>; Vol hippo L – the volume of the left hippocampus in cm<sup>3</sup>; Age onset – age of onset of seizures; AED – number of antiepileptic drugs taken. Diff – difference between LTLE and RTLE patients: for variables sex, handedness and HA values of  $\chi^2$  are presented and for all the others values of Mann-Whitney U test are provided with the corresponding p-value.

	Demographic information			Clinical data						
	Sex	Age	Hand.	EZ lat.	HS	Vol hippo R	Vol hippo L	Age onset	Epilepsy duration	AED
P1	F	54	R (+90%)	Left	No	3.41	3.11	52	2	2
P2	F	37	R (+100%)	Left	No	3.82	4.08	35	2	2
P3	F	32	R (+90%)	Left	Yes	3.01	1.81	29	3	2
P4	M	45	R (+20%)	Left	Yes	3.47	1.97	40	5	5
P5	M	24	R (+100%)	Left	Yes	4.16	2.98	17	7	3
P6	M	24	L (-80%)	Left	Yes	2.04	2.35	16	9	3
P7	M	27	R (+80%)	Left	No	3.99	4.19	21	6	3
P8	F	43	R (+100%)	Left	No	3.92	4.10	12	31	3
P9	F	38	R (+100%)	Left	Yes	3.95	2.58	10	29	3
P10	M	24	R (+40%)	Left	Yes	5.10	3.56	20	4	4
P11	M	28	R (+100%)	Left	Yes	3.37	2.39	1	27	4
P12	F	43	R (+100%)	Right	Yes	2.24	3.71	3	40	6
P13	F	19	L (-100%)	Right	No	3.48	3.46	14	5	3
P14	M	38	R (+100%)	Right	No	3.54	3.82	8	30	2

P15	F	45	R (+100%)	Right	No	3.39	3.18	40	5	2
P16	M	20	R (+90%)	Right	Yes	4.72	4.80	16	4	3
Mean	8F/ (SD)	34 (10.5)	14R/ 2L	11L/ 5R	9	3.60 (0.78)	3.26 (0.86)	20.88 (14.5)	13.06 (13.14)	3.13 (1.15)
Diff.	0.29	29.5	0.37	/	0.78	31	14	37	21.5	30
<i>p</i>	1	.82	1	/	.593	.692	.126	.281	.495	.764

TABLE C.3: Neuropsychological data for TLE patients. The table presents the results of the neuropsychological assessment of language and memory functions carried out by a neuropsychologist and a speech therapist. Abbreviations: VCI – standardized score of verbal comprehension index for verbal semantic memory (Wechsler, 2008); DO80 – standardized score for French version of naming task (Deloche & Hannequin, 1997); SFL – semantic fluency, standardized score of performance on the task of categorical word generation (Godefroy & GREFEX, 2008), PFL – phonological fluency, standardized score of performance on the task of alphabetical word generation (Godefroy & GREFEX, 2008); AMI – standardized score of auditory memory (Wechsler, 2009); IMI – standardized score of immediate memory (Wechsler, 2009); DMI – standardized score for delayed memory (Wechsler, 2009). Standardized scores were considered as pathological if they were equal or lower than -1.65 SD, corresponding to a threshold of  $p \leq 0.05$ . These pathological scores are marked in bold. Diff – difference between LTLE and RTLE patients: values of Mann-Whitney U test are provided with the corresponding p-value.

	Language and memory cognitive scores						
	VCI	DO 80	SFL	PFL	AMI	IMI	DMI
P1	0.00	0.67	1.39	-0.18	0.33	-0.99	-0.28
P2	0.00	-0.30	0.34	-0.30	1.34	-0.47	-0.74
P3	-1.08	<b>-6.43</b>	-0.62	0.24	-1.08	-1.56	-1.41
P4	-0.28	-1.30	-0.67	-1.28	-0.52	-0.08	-0.28
P5	/	-1.30	-0.34	<b>-1.65</b>	/	/	/
P6	-0.41	<b>-2.20</b>	<b>-2.17</b>	-0.97	<b>-2.33</b>	<b>-1.88</b>	<b>-2.33</b>
P7	0.00	-0.03	-0.34	-0.34	1.34	0.13	0.00
P8	0.28	-1.30	-1.65	-1.44	0.09	-0.08	-1.13
P9	-1.56	<b>-5.30</b>	-0.93	-0.32	0.47	0.41	0.08
P10	-0.13	<b>-4.30</b>	1.66	-0.17	0.61	0.47	-0.08
P11	0.28	0.70	-0.24	-1.03	0.67	1.08	1.34
P12	0.13	<b>-2.30</b>	-1.51	-2.02	-1.08	<b>-2.33</b>	<b>-2.05</b>
P13	-1.28	-0.39	-0.37	-0.40	0.67	0.08	-0.61
P14	0.13	<b>-4.30</b>	<b>-1.65</b>	<b>-1.75</b>	0.08	-0.08	-0.28
P15	0.13	-0.30	0.34	-0.30	1.18	1.28	-0.15
P16	0.00	<b>-3.30</b>	<b>-1.73</b>	<b>-1.82</b>	0.33	1.08	0.33
Mean	-0.25	-1.98	-0.53	-0.86	0.14	-0.19	-0.51
(SD)	(0.58)	(2.18)	(1.09)	(0.72)	(1.02)	(1.08)	(0.93)
Diff.	18.5	32	37	42.5	25.5	19.5	25
<i>p</i>	.42	.609	.281	.089	.951	.499	1



TABLE C.4: Descriptive data for movements during resting state and sentence recall task in TLE patients (N = 16) and healthy participants (N = 19). Abbreviations: MVT = movement, Outliers = number of outliers.

State	Measure	Group	Mean	Median	SD	SE	U	<i>p</i>
Resting-state	MVT	Healthy	0.286	0.178	0.244	0.056	196	0.145
		TLE	0.311	0.273	0.180	0.045		
	Outliers	Healthy	20.474	19.000	17.157	3.936	131.5	0.496
		TLE	15.813	14.000	12.276	3.069		
Sentence recall	MVT	Healthy	0.180	0.110	0.198	0.045	189.5	0.214
		TLE	0.156	0.142	0.065	0.016		
	Outliers	Healthy	3.947	2.000	3.488	0.800	107	0.123
		TLE	2.625	0.000	3.981	0.995		

TABLE C.5: Group level modular partition of LMN during resting state and sentence recall task in TLE and HC. The LMN comprises 74 homotopic regions (37 in each hemisphere), as previously described in Roger, Pichat, et al. (2020). The regions are in the space of Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA Joliot et al., 2015). For each of these regions, the module affiliation is provided as well as its moving status. Abbreviations: Rest – resting-state; Recall – sentence recall task; M – mover; DMN – Default Mode Network; FPN – Frontoparietal Network; DAN – Dorsal Attention Network; SAL – Ventral Attention Network; LIMB – Limbic Network; FP – frontoparietal; F – frontal; TLimb – temporo-limbic; FTP1 – Fronto-temporo-parietal 1; FTP2 – Fronto-temporo-parietal 2; TMesial – temporal mesial; TLat – temporal lateral; Ins-cing – insular-cingulate; TP – temporo-parietal.

Region	Network	Healthy Participants			TLE patients		
		Rest	Recall	M	Rest	Recall	M
G_Frontal_Sup_2_L	DMN	FP	F	1	F	F	0
G_Frontal_Sup_2_R	DMN	FP	FP	0	FP	FP	0
S_Sup_Frontal_2_L	FPN	FP	FP	0	FP	FP	0
S_Sup_Frontal_2_R	FPN	FP	FP	0	FP	FP	0
G_Frontal_Mid_1_L	FPN	FTP1	F	1	F	F	0
G_Frontal_Mid_1_R	FPN	F	FP	1	FP	FP	0
S_Inf_Frontal_2_L	FPN	FTP1	FTP1	0	FP	F	1
S_Inf_Frontal_2_R	FPN	F	FP	1	FP	Ins-cing	1
G_Frontal_Inf_Tri_1_L	DMN	FTP2	F	1	F	Ins-cing	1
G_Frontal_Inf_Tri_1_R	DMN	F	F	0	F	Ins-cing	1
G_Frontal_Mid_Orb_2_L	FPN	FP	FP	0	FP	FP	0
G_Frontal_Mid_Orb_2_R	FPN	FP	FP	0	FP	FP	0
G_Frontal_Inf_Orb_1_L	DMN	FTP2	TLimb	1	TLimb	TLimb	0
G_Frontal_Inf_Orb_1_R	DMN	FP	TLimb	1	TLimb	FP	1
G_Frontal_Inf_Orb_2_L	LIMB	TLimb	TLimb	0	TLimb	TLimb	0
G_Frontal_Inf_Orb_2_R	LIMB	TLimb	TLimb	0	TLimb	TLimb	0
S_Precentral_1_L	DAN	FTP1	FTP1	0	FP	F	1
S_Precentral_1_R	DAN	F	F	0	F	Ins-cing	1

S_Precentral_4_L	DAN	F	F	0	F	F	0
S_Precentral_4_R	FPN	F	F	0	F	F	0
G_SupraMarginal_7_L	DMN	FTP2	FP	1	TLat	FP	1
G_SupraMarginal_7_R	DMN	FP	FP	0	FP	FP	0
G_Angular_1_L	DMN	FP	FP	0	FP	FP	0
G_Angular_1_R	DMN	FP	FP	0	FP	FP	0
G_Angular_2_L	DMN	FP	FP	0	FP	FP	0
G_Angular_2_R	DMN	FP	FP	0	FP	FP	0
G_Parietal_Inf_1_L	FPN	FP	FP	0	FP	FP	0
G_Parietal_Inf_1_R	FPN	FP	FP	0	FP	FP	0
S_Intraparietal_2_L	FPN	FP	FTP1	1	FP	FP	0
S_Intraparietal_2_R	DAN	FTP1	FP	1	FP	FP	0
S_Intraparietal_3_L	DAN	FTP1	FTP1	0	FP	TP	1
S_Intraparietal_3_R	DAN	FTP1	FTP1	0	FP	TP	1
G_Insula_anterior_2_L	DMN	F	F	0	F	Ins-cing	1
G_Insula_anterior_2_R	DMN	F	F	0	F	Ins-cing	1
G_Insula_anterior_3_L	SAL	F	F	0	F	Ins-cing	1
G_Insula_anterior_3_R	SAL	F	F	0	F	Ins-cing	1
G_Insula_anterior_4_L	SAL	F	F	0	F	Ins-cing	1
G_Insula_anterior_4_R	SAL	F	F	0	F	Ins-cing	1
G_Temporal_Sup_4_L	DMN	TLimb	FTP1	1	TLat	TLat	0
G_Temporal_Sup_4_R	DMN	TLimb	FTP1	1	TLat	TLat	0
S_Sup_Temporal_1_L	DMN	TLimb	TLimb	0	TLimb	TLimb	0
S_Sup_Temporal_1_R	DMN	TLimb	TLimb	0	TLimb	TLimb	0
S_Sup_Temporal_2_L	DMN	TLimb	FTP1	1	TLat	TLimb	1
S_Sup_Temporal_2_R	DMN	TLimb	TLimb	0	TLat	TLat	0
S_Sup_Temporal_3_L	DMN	FTP2	FTP1	1	TLat	TLat	0
S_Sup_Temporal_3_R	DMN	TLimb	FTP1	1	TLat	TLat	0
S_Sup_Temporal_4_L	SAL	TLimb	FTP1	1	TLat	TLat	0
S_Sup_Temporal_4_R	SAL	TLimb	FTP1	1	TLat	TLat	0
G_Temporal_Mid_3_L	DMN	FTP2	FP	1	TLat	TLat	0
G_Temporal_Mid_3_R	DMN	FTP2	FP	1	TLat	TLat	0
G_Temporal_Mid_4_L	DAN	FTP2	FTP1	1	TLat	TLat	0
G_Temporal_Mid_4_R	DAN	FTP2	FTP1	1	TLat	TLat	0
G_Temporal_Inf_3_L	FPN	FTP1	FTP1	0	FP	TP	1
G_Temporal_Inf_3_R	FPN	FTP1	FTP1	0	FP	TP	1
G_Temporal_Inf_4_L	DAN	FTP1	FTP1	0	FP	TP	1
G_Temporal_Inf_4_R	DAN	FTP1	FTP1	0	FP	TP	1
G_Supp_Motor_Area_2_L	DMN	FP	F	1	F	F	0
G_Supp_Motor_Area_2_R	DMN	F	F	0	F	F	0
G_Supp_Motor_Area_3_L	SAL	F	F	0	F	F	0
G_Supp_Motor_Area_3_R	SAL	F	F	0	F	F	0
G_Cingulum_Ant_2_L	DMN	FP	FP	0	F	Ins-cing	1
G_Cingulum_Ant_2_R	DMN	FP	FP	0	F	Ins-cing	1
G_Cingulum_Post_2_L	DMN	FP	FP	0	FP	FP	0
G_Cingulum_Post_2_R	DMN	FP	FP	0	FP	FP	0
G_ParaHippocampal_2_L	DMN	TLimb	TLimb	0	TLimb	TLimb	0
G_ParaHippocampal_2_R	DMN	TLimb	TLimb	0	TLimb	TLimb	0
G_Fusiform_1_L	LIMB	TLimb	TLimb	0	TLimb	TLimb	0
G_Fusiform_1_R	LIMB	TLimb	TLimb	0	TLimb	TLimb	0
N_Amygdala_1_L	DMN	F	TMesial	1	F	Ins-cing	1
N_Amygdala_1_R	DMN	F	TMesial	1	F	Ins-cing	1
hipp_anterior_L	DMN	TLimb	TMesial	1	TLimb	TLimb	0
hipp_anterior_R	DMN	TLimb	TMesial	1	TLimb	TLimb	0
hipp_posterior_L	DMN	TLimb	TMesial	1	TLimb	TLimb	0

hipp\_posterior\_R                      DMN                      TLimb    TMesial    1                      TLimb    TLimb    0

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TABLE C.6: Lateralization index for frontal lobe, IFG, and temporal lobe during language task for TLE patients and healthy participants. LI was calculated by using the bootstrap method within the LI toolbox for SPM (Wilke & Lidzba, 2007, available at: <https://bit.ly/3kY1L1D>) for frontal lobe, inferior frontal gyrus, and temporal lobe.

Abbreviations: LI – lateralization index, IFG – inferior frontal gyrus.

Participant	Healthy participants			TLE patients		
	LI frontal	LI IFG	LI temporal	LI frontal	LI IFG	LI temporal
1	0.65	0.56	0.68	0.83	0.91	0.55
2	0.79	0.82	0.58	0.53	0.71	0.75
3	0.83	0.62	0.53	0.76	0.66	0.63
4	-0.0003	0.33	-0.07	0.71	0.76	0.53
5	0.54	0.39	0.031	0.82	0.96	0.14
6	0.7	0.71	0.58	0.87	0.77	0.64
7	0.12	0.44	0.2	0.83	0.82	0.35
8	0.7	0.88	0.72	0.86	-0.04	0.38
9	0.76	0.82	0.68	0.56	0.52	0.14
10	0.5	0.63	-0.04	0.94	N/A	0.61
11	0.72	0.63	0.58	0.71	0.74	0.66
12	0.74	0.63	0.56	0.49	0.41	-0.01
13	0.58	0.83	0.56	0.77	0.61	0.64
14	0.85	0.7	0.51	0.53	0.99	0.69
15	0.79	0.67	0.015	0.52	0.24	0.3
16	0.84	0.89	0.81	0.9	0.93	0.81
17	0.67	0.74	0.62			
18	0.44	0.58	0.81			
19	0.53	0.49	0.57			
Mean	0.62	0.65	0.47	0.73	0.67	0.49
(SD)	(0.23)	(0.16)	(0.29)	(0.15)	(0.29)	(0.24)

TABLE C.7: Group level LMN region roles during resting state and RA task in TLE and HC. Abbreviations: Note: Rest – resing-state; Recall – sentence recall task; DMN – Default Mode Network; FPN – Frontoparietal Network; DAN – Dorsal Attention Network; SAL – Ventral Attention Network; LIMB – Limbic Network; Conn. hub – Connector hub. Provinc. hub – Provincial hub, Periph. node – Peripheral node, M – mover.

Region	Network	Healthy participants		TLE patients	
		Rest	Recall	Rest	Recall
G_Frontal_Sup_2_L	DMN	Periph. node	Satellite	Satellite	Satellite
G_Frontal_Sup_2_R	DMN	Provinc. hub	Provinc. hub	Satellite	Periph. node

S_Sup_Frontal_2_L	FPN	Periph. node	Periph. node	Periph. node	Periph. node
S_Sup_Frontal_2_R	FPN	Periph. node	Provinc. hub	Periph. node	Provinc. hub
G_Frontal_Mid_1_L	FPN	Satellite	Satellite	Periph. node	Satellite
G_Frontal_Mid_1_R	FPN	Satellite	Provinc. hub	Provinc. hub	Provinc. hub
S_Inf_Frontal_2_L	FPN	Satellite	Conn. hub	Conn. hub	Conn. hub
S_Inf_Frontal_2_R	FPN	Satellite	Periph. node	Conn. hub	Satellite
G_Frontal_Inf_Tri_1_L	DMN	Conn. hub	Conn. hub	Conn. hub	Conn. hub
G_Frontal_Inf_Tri_1_R	DMN	Conn. hub	Conn. hub	Conn. hub	Conn. hub
G_Frontal_Mid_Orb_2_L	FPN	Satellite	Periph. node	Periph. node	Periph. node
G_Frontal_Mid_Orb_2_R	FPN	Satellite	Periph. node	Provinc. hub	Periph. node
G_Frontal_Inf_Orb_1_L	DMN	Satellite	Conn. hub	Conn. hub	Conn. hub
G_Frontal_Inf_Orb_1_R	DMN	Satellite	Satellite	Satellite	Periph. node
G_Frontal_Inf_Orb_2_L	LIMB	Satellite	Provinc. hub	Conn. hub	Provinc. hub
G_Frontal_Inf_Orb_2_R	LIMB	Satellite	Provinc. hub	Satellite	Conn. hub
S_Precentral_1_L	DAN	Satellite	Satellite	Satellite	Satellite
S_Precentral_1_R	DAN	Conn. hub	Satellite	Conn. hub	Satellite
S_Precentral_4_L	DAN	Satellite	Conn. hub	Satellite	Conn. hub
S_Precentral_4_R	FPN	Conn. hub	Satellite	Satellite	Satellite
G_SupraMarginal_7_L	DMN	Satellite	Periph. node	Satellite	Periph. node
G_SupraMarginal_7_R	DMN	Satellite	Provinc. hub	Satellite	Periph. node
G_Angular_1_L	DMN	Provinc. hub	Provinc. hub	Provinc. hub	Provinc. hub
G_Angular_1_R	DMN	Provinc. hub	Provinc. hub	Provinc. hub	Provinc. hub
G_Angular_2_L	DMN	Provinc. hub	Provinc. hub	Provinc. hub	Periph. node
G_Angular_2_R	DMN	Provinc. hub	Provinc. hub	Provinc. hub	Provinc. hub
G_Parietal_Inf_1_L	FPN	Provinc. hub	Provinc. hub	Provinc. hub	Provinc. hub
G_Parietal_Inf_1_R	FPN	Provinc. hub	Provinc. hub	Provinc. hub	Provinc. hub
S_Intraparietal_2_L	FPN	Satellite	Provinc. hub	Provinc. hub	Periph. node
S_Intraparietal_2_R	DAN	Conn. hub	Periph. node	Provinc. hub	Provinc. hub
S_Intraparietal_3_L	DAN	Conn. hub	Conn. hub	Periph. node	Conn. hub
S_Intraparietal_3_R	DAN	Conn. hub	Satellite	Periph. node	Satellite
G_Insula_anterior_2_L	DMN	Satellite	Satellite	Satellite	Satellite
G_Insula_anterior_2_R	DMN	Conn. hub	Satellite	Satellite	Satellite
G_Insula_anterior_3_L	SAL	Conn. hub	Provinc. hub	Provinc. hub	Provinc. hub
G_Insula_anterior_3_R	SAL	Provinc. hub	Conn. hub	Provinc. hub	Conn. hub
G_Insula_anterior_4_L	SAL	Provinc. hub	Provinc. hub	Provinc. hub	Provinc. hub
G_Insula_anterior_4_R	SAL	Provinc. hub	Provinc. hub	Provinc. hub	Provinc. hub
G_Temporal_Sup_4_L	DMN	Conn. hub	Conn. hub	Satellite	Conn. hub
G_Temporal_Sup_4_R	DMN	Conn. hub	Satellite	Satellite	Conn. hub
S_Sup_Temporal_1_L	DMN	Conn. hub	Conn. hub	Satellite	Conn. hub
S_Sup_Temporal_1_R	DMN	Periph. node	Satellite	Satellite	Satellite
S_Sup_Temporal_2_L	DMN	Conn. hub	Satellite	Satellite	Satellite
S_Sup_Temporal_2_R	DMN	Provinc. hub	Satellite	Satellite	Satellite
S_Sup_Temporal_3_L	DMN	Conn. hub	Conn. hub	Conn. hub	Conn. hub
S_Sup_Temporal_3_R	DMN	Conn. hub	Conn. hub	Conn. hub	Conn. hub
S_Sup_Temporal_4_L	SAL	Conn. hub	Conn. hub	Conn. hub	Conn. hub
S_Sup_Temporal_4_R	SAL	Conn. hub	Satellite	Conn. hub	Conn. hub
G_Temporal_Mid_3_L	DMN	Conn. hub	Satellite	Conn. hub	Satellite
G_Temporal_Mid_3_R	DMN	Satellite	Periph. node	Satellite	Satellite
G_Temporal_Mid_4_L	DAN	Conn. hub	Conn. hub	Satellite	Conn. hub
G_Temporal_Mid_4_R	DAN	Satellite	Satellite	Satellite	Satellite
G_Temporal_Inf_3_L	FPN	Satellite	Satellite	Periph. node	Satellite
G_Temporal_Inf_3_R	FPN	Satellite	Satellite	Periph. node	Satellite
G_Temporal_Inf_4_L	DAN	Conn. hub	Conn. hub	Satellite	Conn. hub
G_Temporal_Inf_4_R	DAN	Satellite	Satellite	Satellite	Conn. hub
G_Supp_Motor_Area_2_L	DMN	Satellite	Conn. hub	Conn. hub	Conn. hub

G_Supp_Motor_Area_2_R	DMN	Satellite	Conn. hub	Provinc. hub	Conn. hub
G_Supp_Motor_Area_3_L	SAL	Satellite	Provinc. hub	Provinc. hub	Conn. hub
G_Supp_Motor_Area_3_R	SAL	Provinc. hub	Provinc. hub	Provinc. hub	Conn. hub
G_Cingulum_Ant_2_L	DMN	Periph. node	Periph. node	Periph. node	Satellite
G_Cingulum_Ant_2_R	DMN	Periph. node	Periph. node	Periph. node	Satellite
G_Cingulum_Post_2_L	DMN	Periph. node	Periph. node	Periph. node	Periph. node
G_Cingulum_Post_2_R	DMN	Periph. node	Periph. node	Periph. node	Periph. node
G_ParaHippocampal_2_L	DMN	Provinc. hub	Satellite	Conn. hub	Provinc. hub
G_ParaHippocampal_2_R	DMN	Provinc. hub	Satellite	Conn. hub	Conn. hub
G_Fusiform_1_L	LIMB	Periph. node	Provinc. hub	Conn. hub	Provinc. hub
G_Fusiform_1_R	LIMB	Periph. node	Satellite	Conn. hub	Conn. hub
N_Amygdala_1_L	DMN	Periph. node	Conn. hub	Periph. node	Periph. node
N_Amygdala_1_R	DMN	Periph. node	Conn. hub	Satellite	Satellite
hipp_anterior_L	DMN	Periph. node	Satellite	Satellite	Periph. node
hipp_anterior_R	DMN	Periph. node	Satellite	Conn. hub	Satellite
hipp_posterior_L	DMN	Periph. node	Satellite	Satellite	Satellite
hipp_posterior_R	DMN	Periph. node	Conn. hub	Satellite	Satellite

TABLE C.8: Role distribution for the regions that changed modules between intrinsic and extrinsic states in TLE and HC. Abbreviations: Rest – resting state; Recall – sentence recall task.

Role	Healthy		TLE	
	Mover regions		Mover regions	
	Rest	Recall	Rest	Recall
Connector hub	11	11	5	7
Provincial hub	0	2	4	3
Satellite	10	11	9	12
Peripheral node	7	4	7	3
Total	28	28	25	25

TABLE C.9: The change of connector hubs within each network between states for HC and TLE patients. Abbreviations: Rest – resting state; Recall – sentence recall task.

		Network					
		DMN	DAN	FPN	SAL	LIMB	
Healthy participants	Mean	Rest	11.42	4.32	3.95	2.79	0.84
		Recall	10.16	2.74	2.63	4.11	1.11
	SD	Rest	2.02	0.93	1.22	0.8	1.61
		Recall	2.59	1.3	0.95	0.99	1.28
	U	140.5	78.5	99.5	246	199	
	$p$	0.24	0.002	0.015	0.052	0.566	
	$pFDR$	0.3	0.011	0.037	0.086	0.566	

TLE patients	Mean	Rest	11.5	1.63	2.5	3.63	1.63
		Recall	9.44	4.56	2.94	4.44	1.13
	SD	Rest	2.13	1.08	1.25	0.95	1.45
		Recall	1.69	1.76	1.46	0.91	1.62
	U	69	227.5	149.5	161	97	
	$p$	0.02	<.001	0.4	0.21	0.23	
$pFDR$	0.062	0.001	0.405	0.282	0.282		

TABLE C.10: Differences between HC and TLE in the state change of connector hubs within each RSN. Abbreviations: HP = healthy participants, TLE = temporal lobe epilepsy patients.

	Mean		SD		Range		U	p	pFDR
	HP	TLE	HP	TLE	HP	TLE			
DMN	-1.26	-2.06	3.74	3.34	-12:3	-7:6	189.5	0.210	0.263
DAN	-1.58	2.94	1.95	2.05	-5:2	-1:7	16.5	<0.001	<0.001
FPN	-1.32	0.438	1.89	2.03	-6:1	-3:5	85	0.022	0.055
SAL	1.32	0.813	2.77	1.83	-4:6	-3:3	177	0.401	0.401
LIMB	0.263	-0.5	1.59	1.21	-3:6	-3:2	194	0.149	0.248

TABLE C.11: Spearman correlation between main network parameters and neuropsychological scores in TLE patients. Abbreviations: Note: VCI – standardized score of verbal comprehension index for verbal semantic memory (Wechsler, 2008); DO80 - standardized score for French version of naming task (Deloche & Hannequin, 1997); SFL – semantic fluency, z core of performance on the task of categorical word generation (Godefroy et al., 2008), PFL – phonological fluency, z score of performance on the task of alphabetical word generation (Godefroy et al., 2008); AMI – standardized score of auditory memory (Wechsler, 2009); IMI - standardized score of immediate memory (Wechsler, 2009); DMI – standardized score for delayed memory (Wechsler, 2009), Nb modules – number of modules.

Network parameter		VCI	DO80	SFL	PFL	AMI	IMI	DMI
Q Rest	rs	0.6	0.25	0.02	-0.47	0.08	0.24	0.27
	$p$	0.017	0.354	0.948	0.07	0.766	0.399	0.326
	$pFDR$	0.119	0.559	0.948	0.245	0.894	0.559	0.559
Q Recall	rs	0.11	0.39	0.26	0.3	0.54	0.32	0.05
	$p$	0.69	0.131	0.332	0.256	0.037	0.249	0.869
	$pFDR$	0.805	0.448	0.465	0.448	0.259	0.448	0.869
Nb modules Rest	rs	0.39	-0.06	-0.13	-0.2	-0.18	0.14	0.2
	$p$	0.152	0.838	0.626	0.467	0.529	0.621	0.469
	$pFDR$	0.73	0.838	0.73	0.73	0.73	0.73	0.73

Nb modules Recall	rs	-0.2	0.17	0.37	0.55	0.42	0.05	-0.21
	<i>p</i>	0.48	0.542	0.155	0.028	0.116	0.873	0.446
	<i>pFDR</i>	0.632	0.632	0.362	0.196	0.362	0.873	0.632
Delta Q	rs	-0.5	-0.06	0.07	0.48	0.15	0.01	-0.2
	<i>p</i>	0.059	0.828	0.803	0.057	0.597	0.975	0.473
	<i>pFDR</i>	0.207	0.966	0.966	0.207	0.966	0.975	0.966
Delta Nb modules	rs	-0.44	0.08	0.36	0.6	0.33	-0.05	-0.27
	<i>p</i>	0.105	0.779	0.169	0.014	0.235	0.87	0.327
	<i>pFDR</i>	0.368	0.87	0.394	0.098	0.411	0.87	0.458
HDI Rest	rs	-0.21	0.23	0.34	0.09	0.28	-0.05	-0.16
	<i>p</i>	0.461	0.391	0.201	0.733	0.307	0.869	0.575
	<i>pFDR</i>	0.805	0.805	0.805	0.855	0.805	0.869	0.805
HDI Recall	rs	0.44	0.34	0.37	-0.03	0.51	0.48	0.51
	<i>p</i>	0.099	0.194	0.161	0.905	0.052	0.073	0.053
	<i>pFDR</i>	0.173	0.226	0.225	0.905	0.17	0.17	0.17

TABLE C.12: Differences between high and low performers on main network parameters. Abbreviations: VCI – standardized score of verbal comprehension index for verbal semantic memory (Wechsler, 2008); DO80 - standardized score for the French version of naming task (Deloche & Hannequin, 1997); SFL – semantic fluency, z core of performance on the task of categorical word generation (Godefroy & GREFEX, 2008), PFL – phonological fluency, z score of performance on the task of alphabetical word generation (Godefroy & GREFEX, 2008); AMI – standardized score of auditory memory (Wechsler, 2009); IMI - standardized score of immediate memory (Wechsler, 2009); DMI – standardized score for delayed memory (Wechsler, 2009), Nb modules – number of modules.

		VCI	DO80	SFL	PFL	AMI	IMI	DMI
Q Rest	U	13	30	29	47	29	17	20
	<i>p</i>	0.142	1	0.753	0.115	0.814	0.327	0.409
	<i>pFDR</i>	0.496	1	0.949	0.496	0.949	0.716	0.716
Q Recall	U	22	9	15	20	13	21	28
	<i>p</i>	0.713	0.023	0.074	0.208	0.099	0.624	0.906
	<i>pFDR</i>	0.832	0.159	0.231	0.363	0.231	0.832	0.906
Nb modules Rest	U	14	32.5	38.5	38.5	30	25.5	21
	<i>p</i>	0.147	0.768	0.458	0.458	0.703	0.947	0.446
	<i>pFDR</i>	0.801	0.896	0.801	0.801	0.896	0.947	0.801
Nb modules	U	29	15	19	12	16.5	33	40.5
	<i>p</i>	0.576	0.059	0.113	0.015	0.157	0.263	0.069
	<i>pFDR</i>	0.576	0.161	0.197	0.103	0.22	0.307	0.161
Delta Q	U	34	23	29	15	20	27	33
	<i>p</i>	0.27	0.448	0.753	0.074	0.409	0.806	0.48
	<i>pFDR</i>	0.671	0.671	0.806	0.519	0.671	0.806	0.671
Delta Nb modules	U	36	21	19	12.5	18	30.5	39
	<i>p</i>	0.147	0.288	0.138	0.026	0.253	0.468	0.128

	<i>pFDR</i>	0.257	0.336	0.257	0.182	0.336	0.468	0.257
HDI	U	31	20	19	21	15	32	35
Rest	<i>p</i>	0.462	0.278	0.172	0.248	0.157	0.391	0.346
	<i>pFDR</i>	0.462	0.456	0.456	0.456	0.456	0.456	0.456
HDI	U	18	15	13	31	13	20	14
Recall	<i>p</i>	0.391	0.104	0.046	0.916	0.099	0.54	0.126
	<i>pFDR</i>	0.548	0.22	0.22	0.916	0.22	0.63	0.22

TABLE C.13: Relation between age and principal network parameters in HC and TLE. Correlation of network parameters with age in healthy participants and TLE patients and the results of ANCOVA with the group as factor and age as a covariate is presented.

Network parameters	Correlation							
	Healthy		TLE		ANCOVA			
	r	p	r	p	F group	p group	F age	p age
Q Rest	0.04	0.867	-0.01	0.965	0.15	0.699	0.24	0.631
Q Recall	-0.22	0.358	-0.17	0.522	0.25	0.623	0.25	0.621
Nb modules Rest	0.09	0.717	0.13	0.631	0.27	0.604	0.27	0.608
Nb modules Recall	-0.13	0.582	-0.2	0.456	0.01	0.920	0.63	0.434
HDI PCs Rest	0.01	0.968	0.06	0.824	81.27	<0.001	0.01	0.974
HDI PCs Recall	0.36	0.125	-0.27	0.319	5.41	0.027	0.60	0.444

TABLE C.14: Network parameter differences between LTLE, RTLE, and HC. Abbreviations: Values of group effect marked with + were obtained using One-way ANOVA with Tukey correction for post-hoc tests for multiple comparisons. The values marked with \* were obtained using the Kruskal-Wallis test because assumptions for ANOVA were not met.

	Q Rest	Q Recall	Nb of modules Rest	Nb of modules Recall	HDI Rest	HDI Recall
LTLE	0.669	0.645	4.18	4.09	-0.677	-0.304
RTLE	0.689	0.684	4.6	4.2	-0.553	-0.212
Healthy	0.673	0.653	4.05	4.26	$-5.04e^{-19}$	$1.10e^{-18}$
Group effect	0.185+	0.755+	2.06*	0.402*	78.1+	7.39+
p	0.832	0.478	0.357	0.818	<.001	0.002
Significant contrasts	/	/	/	/	LTLE >HC RTLE >HC	LTLE >HC



# Appendix D

## Chapter 5 Supplementary material

TABLE D.1: Demographic, clinical, neuropsychological and functional activation characteristics of P1 and P2. Arrows for neuropsychological assessment, responses during recognition of items and LIs indicate the direction of the change after surgery. Neuropsychological changes marked with \* indicate that the change was significantly different (at RCI 90%). Standardized scores were considered as pathological if they were equal or lower than -1.65 SD, corresponding to a threshold of  $p \leq 0.05$ . These pathological scores are marked in bold. LI change marked with \* indicate that the LI of a patient was significantly different in comparison to HC. LI values in bold indicate right lateralization. Abbreviations: LTLE = Left temporal lobe epilepsy; AED = number of epileptic drugs taken; VCI = standardized score of verbal comprehension index for verbal semantic memory (Wechsler, 2008); DO80 = standardized score for French version of naming task (Deloche & Hannequin, 1997); SFL = semantic fluency, z score of performance on the task of categorical word generation (Godefroy & GREFEX, 2008), PFL = phonological fluency, z score of performance on the task of alphabetical word generation (Godefroy & GREFEX, 2008); AMI = standardized score of auditory memory (Wechsler, 2009); IMI = standardized score of immediate memory (Wechsler, 2009); DMI = standardized score for delayed memory (Wechsler, 2009); TMT B-A = standardized score of Trail Making Test B-A (Godefroy & GREFEX, 2008); LI = Lateralization index; GE = sentence generation with implicit encoding; RECO = recognition of items; RA = recall.

	P1	P2
<hr/> Demographic information <hr/>		
Gender	Male	Male
Age	28	45
Education	Vocational high-school	Vocational high-school
Profession	Butcher	Carpenter
<hr/> Epilepsy medical history <hr/>		
Type of epilepsy	Mesial LTLE	Mesial LTLE
Hippocampal atrophy	yes	yes
Age of epilepsy onset	9 months	40 years
Epilepsy duration	27	5
Frequency of seizures	monthly	daily

Number of AEDs	2			4		
Neuropsychological assessment	Before surgery	After surgery		Before surgery	After surgery	
VCI	0.28	0.28	=	-0.28	-0.41	↓
DO-80	0.7	-1.3	↓*	-1.3	<b>-2.3</b>	↓*
SFL	-0.24	-0.62	↓	-0.67	-0.98	↓
PFL	-1.03	-0.71	↑	-1.28	-1.28	=
AMI	0.67	0.88	↑	-0.52	-1.08	↓
VMI	1.56	1.88	↑	0	-0.08	=
IMI	1.08	1.34	↑	-0.08	-0.74	↓*
DMI	1.34	1.65	↑	-0.28	-0.61	↓
TMT B-A	-0.57	-0.28	↑	<b>-2.14</b>	-1.38	↑
Handedness	R (+100%)			R (+20%)		
RECO responses						
Correct	75%	77.5%	↑	80%	72.5%	↓
Incorrect	21.3%	12.5%	↓	16.3%	20%	↑
fMRI – LI						
GE frontal lobe	0.71	0.84	←	0.71	0.29	→
GE temporal lobe	0.66	0.94	←	0.53	0.33	→
GE hippocampi	0.73	/		0.38	/	
RECO frontal lobe	-0.086*	0.67	←	0.081*	0.55	←
RECO temporal lobe	0.41	0.51	←	0.003	-0.43	→
RECO hippocampi	-0.39	/		-0.63	/	
RA frontal lobe	0.59	0.93	←	0.7	-0.24*	→
RA temporal lobe	0.64	0.83	←	0.46	-0.45*	→
RA hippocampi	-0.38	/		0.69	/	

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**Cartographie interactive du langage et de la mémoire chez les patients avec épilepsie focale et pharmaco-résistante. Evaluation multimodale.**

Le présent travail est réalisé dans le cadre de neuroscience cognitive et de la perspective contemporaine des réseaux postulant que les fonctions neurocognitives n'existent pas et n'agissent pas de manière isolée, mais dans le contexte d'autres fonctions et que les processus cognitifs sont représentés par des réseaux cérébraux. En lien avec ces notions, cette thèse visait à explorer l'interaction entre le langage et la mémoire. Ainsi, nous nous sommes principalement concentrés sur le langage, tout en nous intéressant au rôle de soutien de la mémoire. La connexion entre le langage et le système de mémoire déclarative est particulièrement précieuse car ils partagent un domaine - la sémantique. Nous nous sommes particulièrement intéressés à la manière dont cette interaction langage-mémoire est soutenue au niveau neuronal. En outre, les preuves de l'interaction langage-mémoire proviennent des découvertes concernant les patients atteints d'épilepsie du lobe temporal (TLE). Le réseau épileptogène de ces patients est concentré sur le lobe temporal et est généralement suivi d'une sclérose de l'hippocampe. Les études contemporaines ont montré que cette région et le lobe temporal, en général, sont à l'intersection du langage et de la mémoire. Ces patients constituent donc un modèle d'étude de l'interaction langage-mémoire. Plus précisément, comment elle est réorganisée chez ces patients si la principale ligne de communication entre eux est endommagée et quelles en sont les conséquences cognitives. L'objectif du projet REORG dans le cadre duquel cette thèse a été réalisée était de fournir des réponses à ces questions et des outils pratiques pour la pratique clinique.

Pour explorer l'interaction langage-mémoire, nous avons besoin d'un outil adéquat capable de capturer cette synergie en action tout en étant adapté à la fois aux contextes cliniques et aux normes de recherche empirique. Dans ce but, le protocole GE2REC a été développé dans le cadre du projet REORG pour la cartographie interactive du réseau langage-mémoire (LMN).

Sa reconfiguration est basée sur le changement de communication entre les différents sous-réseaux qui composent le LMN comme un méta-réseau. Les patients atteints de TLE présentent différentes réorganisations intra- et inter-hémisphériques de ce réseau, bien que leur LMN comprenne généralement des régions similaires à celles des individus sains. De plus, sa réorganisation chez les patients TLE se traduit par une reconfiguration différente entre l'état et les contextes externes. Globalement, les mécanismes d'intégration du LMN sont modifiés dans la TLE.

Sur la base de nos résultats, nous avons proposé un modèle neurocognitif de l'interaction entre le langage et la mémoire qui peut être résumé comme suit. Dans un contexte de communication, la mémoire déclarative soutient le langage afin que nous puissions nous disloquer du temps et de l'espace dans notre conversation et façonner notre message pour qu'il soit compréhensible par nos interlocuteurs. Les processus interactifs cruciaux se déroulent au niveau des "tampons épisodiques" - l'un basé sur les structures temporelles mésiales et l'autre sur le réseau frontopariétal. Sur la base de ces tampons, les éléments sémantiques et épisodiques sont liés dans l'expérience et les représentations qui façonnent nos énoncés. Cette relation devient encore plus évidente lorsque le LMN des patients atteints de TLE est exploré, car ces patients ont une fonctionnalité réduite du tampon hippocampique standard. Les autres

régions du système de mémoire déclarative prennent le relais des fonctions de la région endommagée, et les systèmes de contrôle cognitif s'engagent davantage dans l'intégration du réseau. Par conséquent, les patients atteints de TLE présentent des déficits de mémoire épisodique et/ou de récupération lexicosémantique (dénomination).

Nous concluons notre travail en discutant et en illustrant l'importance d'explorer cette interaction dans le cadre de l'évaluation pré-chirurgicale des patients atteints de TLE. De plus, nous présentons comme perspectives de ce travail la prédiction multimodale du résultat cognitif post-chirurgical chez les patients atteints de TLE. Notre travail suggère que les fonctions cognitives complexes et interactives, telles que le langage et la mémoire déclarative, devraient être étudiées de manière dynamique, en tenant compte de l'interaction entre les réseaux cognitifs et corticaux.