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Multimodal approach of reward processing vulnerabilities in mesial Temporal Lobe Epilepsy Surgery

Myriam Gricelda De la Cruz Puebla

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Multimodal approach of reward processing vulnerabilities in mesial Temporal Lobe Epilepsy Surgery

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DEDICATORIA

A mi amado **Danny**, por ser no solo quien me ha motivado a hacer mis sueños realidad, sino quien me ha tomado de la mano para trabajar juntos por ellos.

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LIST OF ABBREVIATIONS

^{18}F-FDG	^{18}F-Fluorodeoxyglucose
AEDs	Antiepileptic Drugs
AH	Affected Hemisphere
AI	Asymmetry index
AMPA	Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
AMPAR	Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor
AMTL-N400/P600	Anterior Mesial Temporal Lobe-N400/P600
AR(1)	Autoregressive model of order 1
ASDs	Antiseizure Drugs
ATL	Anterior temporal lobectomy
BDI	Beck Depression Inventory
BOLD	Blood Oxygen Level Dependent
BPD	Borderline Personality Disorder
CA	Cornu Ammonis
CBD	Cannabidiol
Cho	Choline
cmPFC	Central Medial Prefrontal Cortex
CNS	Central Nervous System
Cr	Creatine
CSC	Cuneiform/Subcuneiform Nuclei
CT	Computed Tomography
D1	Dopamine receptor 1
D2	Dopamine receptor 2

DALYs	Disability-adjusted life-years
DBS	Deep Brain Stimulation
DDT	Delayed Discounting Task
DG	Dentate Gyrus
DGe	External limb of the dentate gyrus
DGi	Internal limb of the dentate gyrus
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
dmPFC/ACC	Dorsomedial Prefrontal/Anterior Cingulate Cortex
DOA	Disorders of Arousal
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
ENT	Equilibrative Nucleoside Transporter
EPI	Echo-planar imaging
EROs	Event-related oscillations
ERPs	Event-related brain potentials
FA	Fractional Anisotropy
FASs	Focal aware seizures
FDR	False Discovery Rate
FIAS	Focal impaired awareness seizures
fMRI	Functional Magnetic Resonance Imaging
FN400	Frontal Negativity (a component of ERP)
FRN	Feedback-Related Negativity
FSG	Superior Frontal Gyrus
GABA	Gamma-Aminobutyric Acid

GABA-A	Gamma-Aminobutyric Acid Type A Receptor
GABA-B	Gamma-Aminobutyric Acid Type B Receptor
GABA	Gamma-Aminobutyric Acid
GAT	GABA Transporter
GCD	Granule Cell Dispersion
GDT	Game of Dice Task
GFAP	Glial Fibrillary Acidic Protein
GMV	Gray matter volume
GPR55	G Protein-Coupled Receptor-55
H&E	Hematoxylin and Eosin
HFOs	High-frequency oscillations
HS	Hippocampal Sclerosis
IAT	Intracarotid Amobarbital Test
IEDs	Interictal Epileptiform Discharges
iEEG	Intracranial Electroencephalography
IFG	Inferior Frontal Gyrus
IGT	Iowa Gambling Task
ILAE	International League Against Epilepsy
LGS	Lennox-Gastaut Syndrome
LITT	Laser Interstitial Thermal Therapy
LmTLE-HS	Left-sided Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
LPC	Late Positive Potential
LPN	Late posterior negativity
LTLE	Left Temporal Lobe Epilepsy

MAGs	Meta-Analytic Groupings
MD	Mean Diffusivity
MEG	Magnetoencephalography
MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex
MPRAGE	Magnetization-prepared rapid-acquired gradient echo
MRI	Magnetic Resonance Imaging
MTL-P300	Mesial Temporal Lobe-P300
mTLE	Mesial Temporal Lobe Epilepsy
mTLE-HS	Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
MTS	Mesial Temporal Sclerosis
NAA	N-acetil aspartate
NAcc	Nucleus Accumbens
NAEC	National Association of Epilepsy Centers
NeuN	Neuronal Nuclei
NMDA	N-Methyl-D-Aspartate
OFC	Orbitofrontal Cortex
PCC	Posterior Cingulate Cortex
PCUN	Precuneus
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PGT	Probabilistic Gambling Task
PMGT	Probabilistic Monetary Gambling Task
PNES	Psychogenic Non-Epileptic Seizures
PPN	Pedunculopontine Tegmental Nucleus

pSTS	Posterior Superior Temporal Sulcus
QOL	Quality of Life
ReHo	Regional Homogeneity
REM	Rapid Eye Movements
RmTLE-HS	Right-sided Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
RNS	Responsive Neurostimulation
ROI	Region of Interest
RP	Reward Processing
RPEs	Reward Prediction Errors
SC	Subiculum
SEEG	Stereoelectroencephalography
SET	Scene Encoding Task
SHAPS	Snaith-Hamilton Pleasure Scale
SLF	Superior longitudinal fasciculus
SN	Salience Network
SPECT	Single-Photon Emission Computed Tomography
SPM12	Statistical Parameter Mapping
SQUIDs	Superconducting Quantum Interference Devices
STG	Superior Temporal Gyrus
SUB	Subiculum
SUDEP	Sudden Unexpected Death in Epilepsy
T1	T1-weighted Sequence
T2	T2-weighted Sequence
T2	T2-Weighted Sequence

TBSS	Tract-Based Spatial Statistics
tDCS	Transcranial direct current stimulation
TLE	Temporal Lobe Epilepsy
TMS	Transcranial Magnetic Stimulation
TRPV	Transient Receptor Potential Vanilloid
UH	Unaffected Hemisphere
VBM	Voxel-Based Morphometry
VEEG	Video Electroencephalography
vmPFC	ventromedial prefrontal cortex
VNS	Vagus Nerve Stimulation
VTA	Ventral Tegmental Area
WHO	World Health Organization
WM	Working Memory

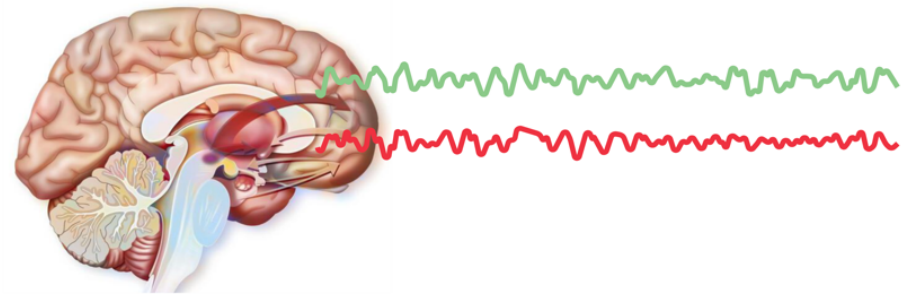
SUMMARY

This study investigated the neural correlates of reward processing (RP) in patients with mesial temporal lobe epilepsy due to unilateral hippocampal sclerosis (mTLE-UHS) before and after epilepsy surgery. The study utilized functional Magnetic Resonance Imaging (fMRI) and electroencephalogram (EEG), including event-related potentials (ERPs) and event-related oscillations (EROs). The study involved mTLE-UHS patients and healthy controls. Participants underwent EEG (first study) and fMRI scans (second study) pre- and post-surgery (for patients) or longitudinally (for controls). The EEG study employed various behavioral tasks, including the Iowa Gambling Task (IGT), Game of Dice Task (GDT), and a probabilistic gambling task (PGT) and Neuropsychological evaluation.

Pre-surgically, at the behavioral level, mTLE-UHS patients exhibited impairments in decision-making under ambiguity, as evidenced by their performance on the IGT but not under conditions of risk (GDT). At the neuropsychological level, they showed deficits in verbal comprehension, verbal memory, visuospatial memory, and working memory. At the electrophysiological level, mTLE-UHS patients exhibited disruptions in feedback-related negativity (FRN) and reduced parietal delta and frontal theta activity in the EEG component. Post-surgically, behaviorally, there were improvements in task performance, but not to the level of controls. Neuropsychologically, patients showed continued deficits in the cognitive domains described previously. Finally, EEG data indicated a significant interaction between group and evaluation, showing altered neural responses in mTLE-UHS patients compared to controls.

For the fMRI component, pre-surgical mTLE-UHS patients showed reduced activity in the unaffected hemisphere's amygdala, insula, superior temporal gyrus, and dorsolateral prefrontal cortex during gain and loss processing. The affected hemisphere's superior frontal gyrus had reduced activity during loss processing. Post-surgical fMRI data discerning the interaction effect between groups and evaluations revealed higher neural activation in the mTLE-UHS group compared to controls in areas such as the orbitofrontal cortex, ventromedial prefrontal cortex, and nucleus accumbens, regardless of outcome valence. No significant behavioral differences were observed between groups or sessions.

The EEG study revealed that mTLE-UHS is associated with disrupted feedback processing, as evidenced by altered FRN and reduced parietal delta and frontal theta activity, both pre- and post-surgery. These findings suggest difficulties in processing and utilizing feedback information effectively. The fMRI study showed altered brain activation patterns in reward-related circuitry before and after epilepsy surgery. Post-surgical changes, especially in the affected hemisphere, might reflect compensatory mechanisms or neuroplastic reorganization. The disparity between neural and behavioral findings underscores the complexity of neural alterations and cognitive outcomes in mTLE-UHS. Further research is essential to understand the long-term impact of these changes on cognitive function, emotional regulation, and overall well-being, which is crucial for developing targeted interventions.



CHAPTER I: INTRODUCTION

1. INTRODUCTION

Epilepsy stands as one of the most prevalent neurological disorders (1,2). According to the World Health Organization, the current estimate suggests that approximately 50 million individuals worldwide are affected by this condition, with an annual diagnosis of 5 million new cases (3). From a pathophysiological standpoint, the epileptic seizures origin lies in the abnormal discharge of a specific group of neurons (4). Consequently, the clinical manifestations depend on the location of this aberrant neuronal population and the spread of this electrical activity, which can affect adjacent structures as well as more distant ones, both within the same cerebral hemisphere and across the contralateral hemisphere (5).

Although we use the term "epilepsy" to encompass all conditions that meet the criteria of recurrent unprovoked seizures, due to the complexity and diversity of its clinical presentations, epilepsy has been classified based on various factors for comprehensive diagnostic and therapeutic approaches. These factors include the age of onset, the type of seizures, the presence or absence of demonstrable lesions, and the etiology of the condition (6). In light of these last two factors, the most common form of focal epilepsy in children and adults is mesial temporal lobe epilepsy (7), often closely associated with histopathological findings such as hippocampal sclerosis (8). This condition is characterized by neuronal loss and its subsequent replacement by glial cells, a process known as gliosis (9).

The structural alteration resulting from this condition and its functional consequences impacts other brain structures beyond the mesial temporal lobe, suggesting a more widespread disruption of interconnected neural networks rather than a strictly focal

condition. Structures involved include the hippocampi, amygdala, entorhinal cortices, lateral temporal neocortices, medial thalamus, and inferior frontal lobes among others (10–15). The specific locations of these structures and their intricate connections with cortical and subcortical regions highlight the potential for widespread disruption across multiple cognitive domains. For example, the hippocampus, a key structure for memory formation, is often affected in mTLE-UHS, leading to difficulties in encoding and retrieving information, particularly episodic memories (16–19). Additionally, alterations in the amygdala, a crucial component of the emotional processing network, can contribute to anxiety, depression, and difficulties regulating emotions in patients with mTLE-UHS (20,21). Attention, another essential cognitive function, can also be impaired, potentially due to disruptions in the prefrontal cortex, which plays a role in executive functions, including attention and planning (17,22,23). Language abilities, including fluency, comprehension, and object naming, may be affected due to involvement of the lateral temporal cortex (24).

While these cognitive systems have been extensively studied in the context of mTLE-UHS, other interconnected networks remain less well understood. For instance, the reward system (25), a crucial network involved in decision-making, learning based on the analysis of the consequences of actions, and various cognitive functions, is also likely to be affected by this condition. Its impact on behaviors, motivation, and overall well-being requires further investigation. Understanding this system's dysfunction could shed light on the susceptibility of individuals with mTLE-UHS to experience a wide range of cognitive (26), behavioral, and affective symptoms, including those associated with depression, such as anhedonia (27).

The complex and intertwined anatomical and functional relationship between mesial temporal lobe epilepsy with hippocampal sclerosis and the reward system underscores the importance of precisely elucidating the consequences at this level, both concerning the condition itself and the outcomes following surgical resection of the epileptogenic lesion.

To gain a more comprehensive understanding of this relationship, this doctoral thesis will delve into both general and specific aspects, aiming to provide a scientifically grounded explanation for this intriguing phenomenon.

1. Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (mTLE-HS): Comprehensive synthesis from foundational concepts to advanced insights

The definition and conceptualization of mesial temporal lobe epilepsy with hippocampal sclerosis have evolved significantly within the framework established by the International League Against Epilepsy (ILAE). The ILAE's 1981 compendium first employed the term mesial temporal lobe epilepsy to categorize focal epilepsies originating from this specific cerebral region, yet without any reference to hippocampal sclerosis (28). It was in the 1989 publication that this terminology was consistently used to describe such focal epilepsies, still without mention of hippocampal sclerosis.

A pivotal shift occurred in the ILAE's 1993 revision, which marked the inaugural inclusion of mesial temporal lobe epilepsy with hippocampal sclerosis as a term (29). This iteration underscored the correlation between seizures emanating from the mesial temporal lobe and structural changes within the hippocampus. The ILAE's 2010 revision preserved this nomenclature and incorporated additional criteria to define this epilepsy

variant more precisely, stressing the diagnostic significance of hippocampal sclerosis (28). This designation has been steadfast, echoed in the 2014 (30) and 2017 (31) communications currently used in clinical practice and research.

Presently, expert opinions have argued the validity of classifying mTLE-HS as an epileptic syndrome (32), a debate underpinned by several arguments. One critical rationale is the diagnostic's pivotal role in formulating effective treatment strategies and its correlation with disease prognosis (33). Another supporting argument is that it fulfills the criteria to be classified as such: a distinctive set of clinical and EEG characteristics, often corroborated by specific etiological findings(33) (genetic, infectious, structural, immune, and metabolic).. These aspects should be clarified in the near future, given their importance in the comprehensive management of the disorder. Meanwhile, the diagnosis will continue to rely on the latest guidelines published by the ILAE in 2017.

Currently, a promising approach is the multi-omic analysis, combining genomics, transcriptomics, proteomics, and metabolomics. These studies reveal genetic variants, gene expression changes, protein alterations, and metabolic disturbances underlying mTLE-HS. By integrating data from these disciplines, researchers can identify biomarkers for early diagnosis, prognostic markers, and personalized treatment targets (34). Figure 1 illustrates the publication trends over the past two decades concerning various omics approaches in mTLE-HS.

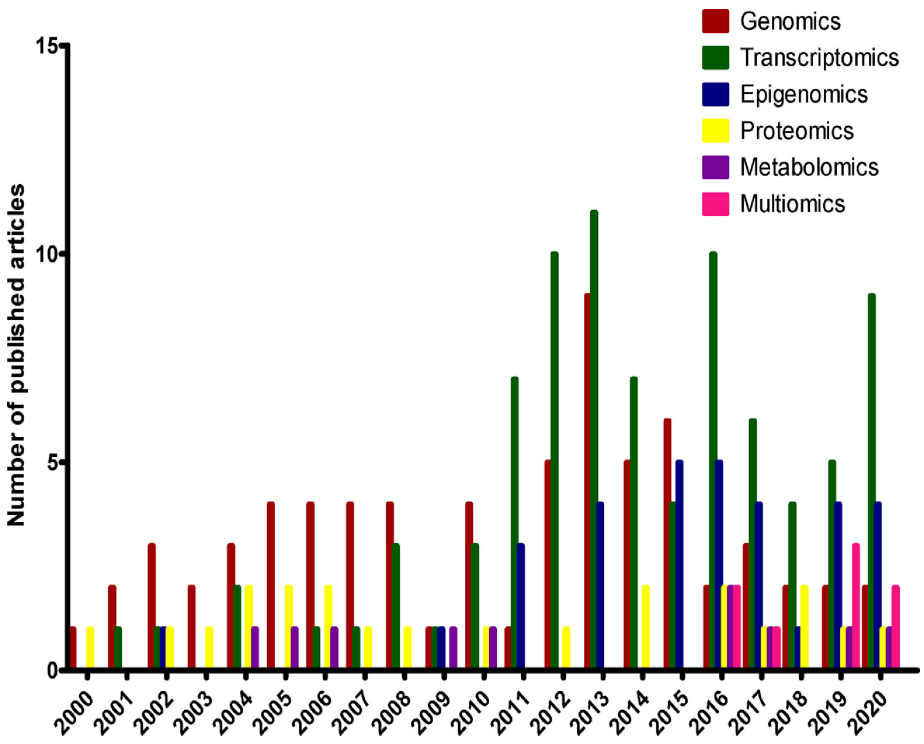


Figure 1. The count of articles published employing diverse omics methodologies for investigating mesial temporal lobe epilepsy. From Bruxel et al. (2021) (34)

Therefore, to grasp the complexity of arriving at this diagnosis, it is crucial to recapitulate some general aspects of epilepsy, the fundamental concepts involved in its diagnosis, and the current levels that serve as guidelines for its management.

1.1. Epilepsy: Definitions and general considerations

Clinical epileptic seizure: Is defined as the anomalous synchronized neuronal activity in the brain, resulting in temporary clinical signs or symptoms. The components of an epileptic seizure encompass: (i) the way it starts and ends, (ii) its clinical expressions, and (iii) the presence of heightened abnormal synchrony (35). Because it is a brief occurrence, a seizure should have a well-defined commencement and cessation.

Accurate diagnosis of epileptic seizures is crucial but challenging due to their varied clinical presentations. Differential diagnoses must consider various paroxysmal events and age-related factors (36). Understanding these differences is vital for optimal management. Tables 1 and 2 below summarize the list of potential differential diagnoses based on clinical manifestations and age considerations.

Table 1. Main clinical features of epileptic seizures and their differential diagnoses. From Leibetseder et al. (2020) (36).

Loss of awareness/consciousness	Convulsions (generalized)	Paroxysmal events during sleep	Drop attacks	Focal symptoms
Syncope	Syncope	REM-sleep behavior disorder	Syncope	Transient ischemic attack
PNES	PNES	Sleep apnea syndrome	Acute brainstem disorder	Movement disorder
Panic attack, hyperventilation	Movement disorder, e.g. Chorea	Restless legs syndrome	Cataplexia	Migraine
Hypoglycemia	Hypoxia	Sleep myoclonus	Metabolic disorder, f.e. periodic paralysis	Psychiatric disorder
Sleeping disorder, e.g. narcolepsy	DOA	DOA		Tic
DOA				Inflammatory brain disease

Rapid eyes movements (REM); psychogenic non-epileptic seizures (PNES); Disorders of arousal (DOA)

Table 2. Paroxysmal non-epileptic events/disorders according to age (<18 years). From Leibetseder et al. (2020) (36).

Newborn	Infancy and childhood	Adolescent
Benign sleep myoclonus	Breath-holding spells	Syncope
Jitteriness	Self -gratification behaviour (masturbation, head rolling)	Sleep disorders
Hyperekplexia	Shuddering / shivering attacks Stereotypes Benign paroxysmal torticollis Benign paroxysmal tonic upward gaze Benign paroxysmal vertigo Sleep disorders Spasmus nutans Sandifer syndrome Tics	Psychogenic non-epileptic events Tics Migraine

Epilepsy: Is a multifaceted neurological disorder which is characterized by the recurrent occurrence of unprovoked seizures due to aberrant neuronal activity within the brain (3). As per the guidelines established by the ILAE, epilepsy is characterized by any of the following conditions: **i)** the occurrence of a minimum of two unprovoked seizures (or reflex seizures) with an interval of more than 24 hours between them**; ii)** the presence of a single unprovoked seizure (or reflex seizure) along with a likelihood of subsequent seizures akin to the general recurrence risk, which amounts to at least 60% after two unprovoked seizures have transpired within the subsequent decade; and **iii)** the confirmation of an epilepsy syndrome (30). Nevertheless, for the purposes of conducting population-based research, the ILAE Epidemiology Commission recommends defining epilepsy as the manifestation of two or more unprovoked seizures separated by at least a 24-hour interval (37).

Epidemiology: Epilepsy poses a considerable global health dilemma, impacting approximately between 48 and 65 million people on a global scale (37,38). It is a condition that transcends age groups, geographical boundaries, and socioeconomic strata (39,40). The prevalence of epilepsy varies significantly across nations, influenced by a myriad of factors including demographic features, diagnostic criteria, and access to healthcare services (39,41). The incidence of epilepsy also exhibits disparities, with a higher occurrence in regions classified as low/middle-income as opposed to high-income areas Figure 2 (42). This divergence can be attributed to a range of factors, encompassing perinatal risk elements, infectious maladies, and traumatic brain injuries. While epilepsy, on the whole, carries a relatively modest mortality risk, specific subgroups such as children and individuals experiencing symptomatic seizures face an elevated mortality rate (43). Of notable concern is sudden unexplained death in epilepsy (SUDEP), primarily associated with generalized tonic-clonic seizures and nocturnal seizures (39). Beyond its

impact on mortality, epilepsy imposes a substantial burden on both individuals and society as a whole, contributing to the calculation of disability-adjusted life-years (DALYs) and exerting adverse effects on overall quality of life (38) Figure 2 . This epidemiological panorama underscores the critical necessity of comprehending the intricate facets of epilepsy to inform research, healthcare strategies, and public health initiatives.

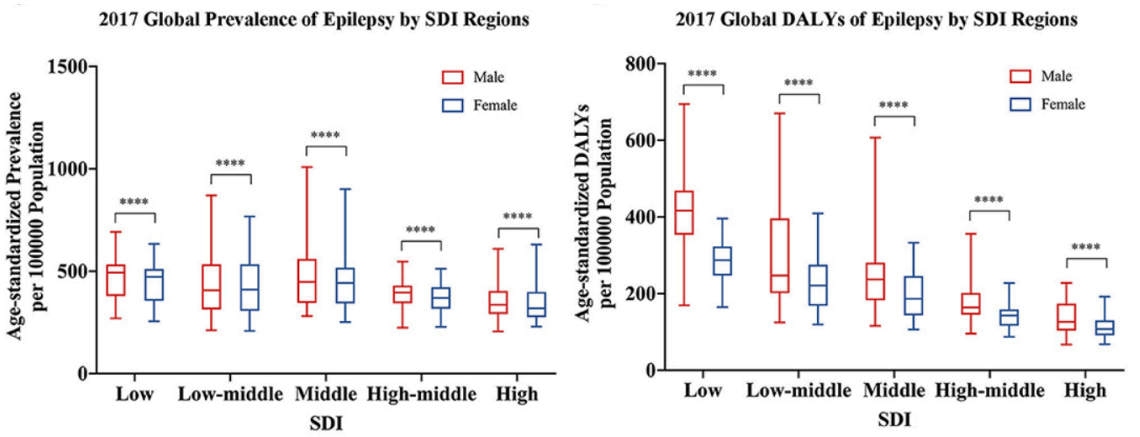


Figure 2. The distribution of epilepsy burden across various socio-demographic index (SDI) regions in 2017, with a focus on gender-specific differences. **(A)** Standardized prevalence rates across different SDI groups are depicted, taking into account age and sex, **(B)** The age-standardized disability-adjusted life year (DALY) rates across different SDI groups are also presented, considering both age and sex. Statistical significance between genders is denoted by ****$p < 0.0001$, as determined by paired Wilcoxon signed rank test. Modified rom Yin et. al (2021) (44).

Clinical manifestations: Epileptic seizures represent the hallmark clinical manifestation of epilepsy. These seizures are transient episodes of abnormal, synchronous, and excessive neuronal firing within the cerebral cortex (45). Seizure manifestations can vary widely, encompassing alterations in consciousness, motor activity, sensory perception, and autonomic function (45). The diverse clinical presentations of epilepsy underscore the complexity of the disease, which may range from brief, subtle focal seizures to convulsive generalized tonic-clonic seizures.

Pathophysiology and etiology: Seizures arise when there is an aberrant synchronized discharge of neurons within a specific brain region or across the entire brain, often resulting from irregularly configured neural networks or disruption caused by structural, genetic, immune, infectious, or metabolic disturbances (35). Among pediatric patients, the predominant causes of seizures encompass genetic predisposition, perinatal insults leading to injury, and anomalies in cortical development (46). In contrast, among adults lacking a genetic susceptibility to epilepsy, common underlying factors for seizures comprise conditions such as encephalitis, meningitis, traumatic brain injury, and brain tumors (46). Among elderly individuals, epilepsy typically emerges as a consequence of primary neurodegenerative disorders, head trauma, or brain neoplasms (46). However, despite all the mentioned etiologies within each age group, there still exists a significantly high percentage of epilepsies with an unknown etiology. This variance in the etiology of epilepsy across distinct age groups contributes to a bimodal distribution in the prevalence of the condition, with genetic and developmental factors peaking during childhood, while accumulated brain injuries, such as those resulting from trauma or tumors, peak in the elderly population. Figure 3 shows the epilepsy etiologies in European region.

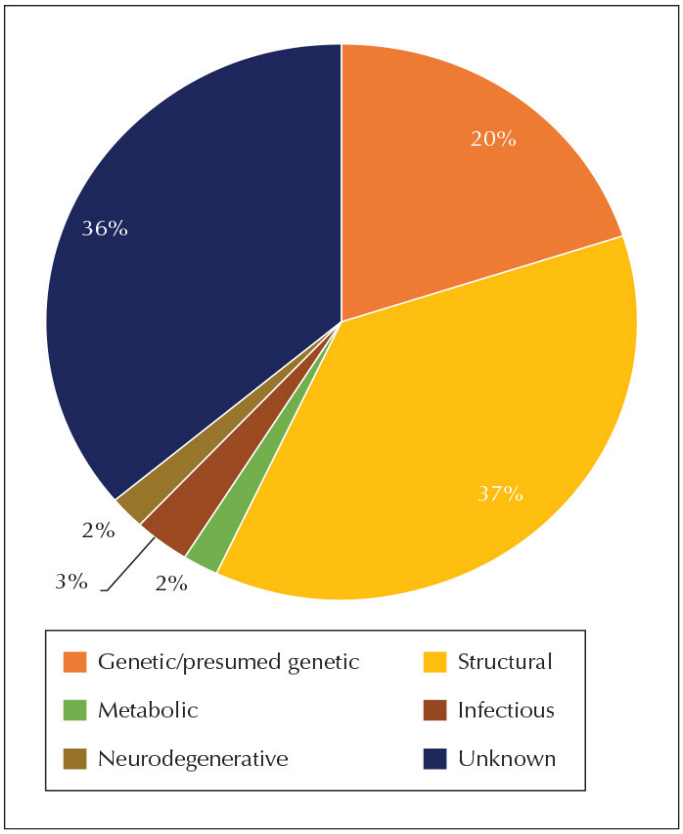


Figure 3. Causes of epilepsy in a well-resourced European area. From Balestrini et. al (2021) (46).

These diverse underlying causes lead to the common pathophysiological mechanism of neuronal hyperexcitability and hypersynchronization.

1.1.1.Classification and diagnosis

Seizure classification

In the context of seizure classification, two primary classifications are available: the basic classification and the expanded classification.

The basic classification primarily centers around the onset of seizures, classifying them into four categories: **1) focal:** when It initiates from a specific focal point; **2) generalized:**

when there is the simultaneous activation of both brain hemispheres at the seizure's outset; **3) unknown:** when historical data and supporting studies like MRI, CT, and EEG fail to ascertain whether the seizure is focal or generalized, or **4) unclassifiable:** when it does not fit in the previous categories (3,45). Once the onset type is determined, the next critical distinction is whether the seizure affects consciousness. Two options exist for this designation: **1) aware** or **2) impaired awareness:** If consciousness is compromised, the seizure falls under the category of an impaired awareness seizure. If not, it is labeled as an aware seizure. This awareness terminology is closely linked to the onset type, giving rise to distinctions like focal aware seizures (FASs) and focal impaired awareness seizures (FIAS). These new terms replace the previous nomenclature of simple partial seizures and complex partial seizures to eliminate the misleading perception of simplicity or complexity associated with awareness levels (3,47) (Figure 4).

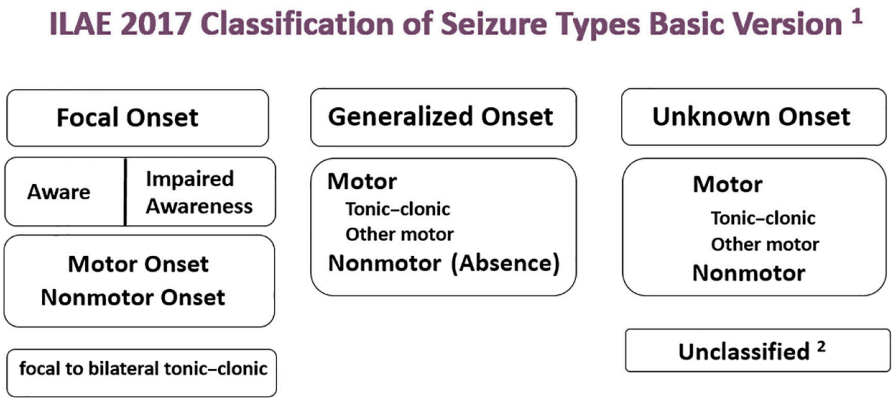


Figure 4. The basic ILAE 2017 operational classification of seizure types. From Fisher et al. (2017) (45).

On the other hand, the expanded classification offers more detailed classifiers within both motor and nonmotor classifications, based on the initial symptom or sign displayed during the seizure (3).

The expanded classification of seizures (Figure 5) enhances the basic classification by offering more detailed subcategories within both the motor and nonmotor classifications. Whenever feasible, it is advisable to employ these more detailed subcategories. These subcategories are determined based on the initial symptom or sign displayed by the individual experiencing the seizure. It is essential to recognize that this initial symptom may not necessarily be the most prominent feature. The only exception to this rule pertains to the behavioral arrest type, where behavioral arrest must be the prevailing feature throughout the entire duration of the seizure. If a specific seizure does not neatly align with any of these subcategories, it is recommended to utilize the most appropriate subcategory available or introduce additional descriptors to provide a more comprehensive account of the seizure (45).

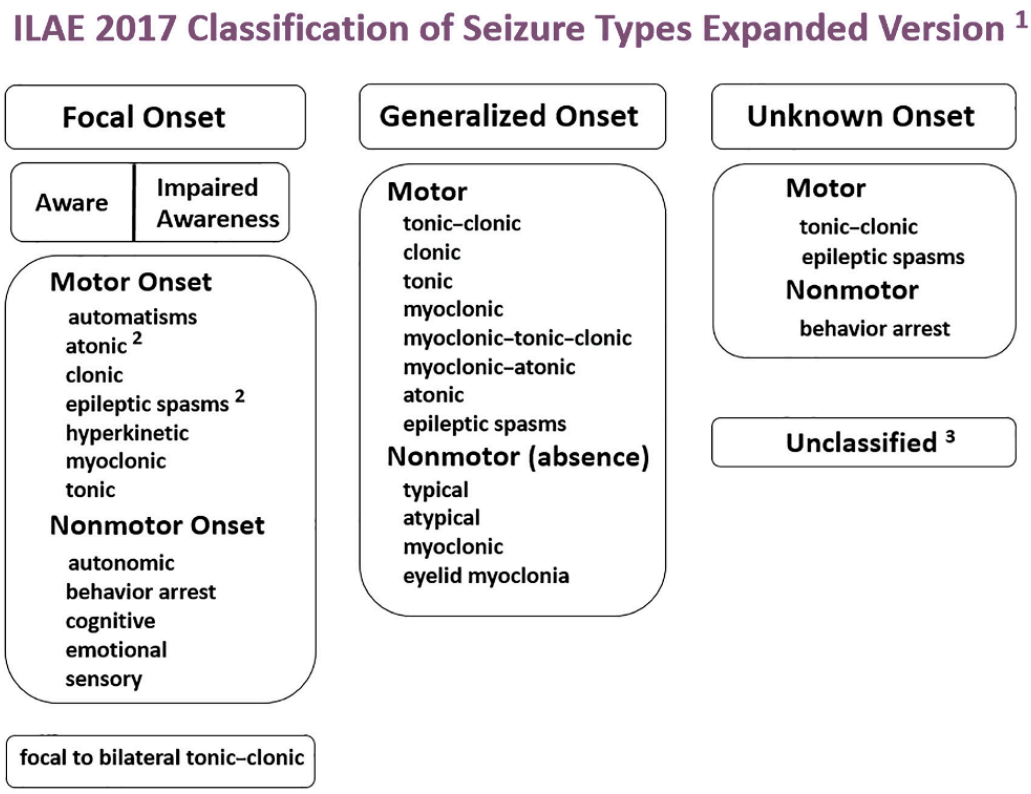


Figure 5. The expanded ILAE 2017 operational classification of seizure types. From Fisher et al. (2017) (45)

Epilepsy classification

The classification of epilepsy is a complex endeavor that hinges upon multiple factors, including clinical presentation, electroencephalographic findings, neuroimaging results, and etiological considerations (47). The ILAE classifies epilepsies into various syndromes and types based on clinical and electroencephalographic (EEG) features. This classification system aids in precise diagnosis and treatment selection, highlighting the heterogeneity of epileptic disorders (6).

The intricacies involved in classifying epilepsy have led the ILAE to introduce a comprehensive multilevel classification system in their most recent Epilepsy

classification update. This system is designed to accommodate the diverse clinical environments worldwide, taking into account differences in available resources.

First level of classification

The cornerstone of the Epilepsy classification framework revolves around categorizing Seizure Types. It assumes that clinicians have already definitively diagnosed an epileptic seizure and does not serve as a diagnostic algorithm for distinguishing epileptic events from non-epileptic ones (6).

Second level of classification

The second level of classification, assumes the patient has already received an epilepsy diagnosis based on the 2014 definition. This level introduces a new category, Combined Generalized and Focal Epilepsy, alongside the established categories of Generalized Epilepsy and Focal Epilepsies, with an additional Unknown category.

Generalized Epilepsy is characterized by generalized spike-wave activity on EEG and encompasses various generalized seizure types. Focal Epilepsies consist of unifocal and multifocal disorders, with different seizure types observed. The Combined Generalized and Focal Epilepsies category addresses patients experiencing both generalized and focal seizures. Diagnosis relies on clinical assessment supported by EEG findings. The term "Unknown" is used when insufficient information is available to determine the epilepsy type (3,6).

Following the determination of the epilepsy type, the next step is to identify its etiology. Etiologies of epilepsy, as defined in the classification system, include structural, genetic, infectious, metabolic, immune, and unknown factors. It is important to note that a patient may have multiple etiologies, and these factors are not hierarchical in nature (3,6,39,46,47).

Third level of classification

Involves diagnosing an Epilepsy Syndrome. This refers to a set of characteristics encompassing seizure types, EEG and imaging features, often linked by age-related factors like onset, remission (if applicable), triggers, diurnal patterns, and sometimes prognosis. Epilepsy Syndromes may also include unique co-existing conditions such as intellectual and psychiatric impairments, specific EEG and imaging findings, and implications for etiology, prognosis, and treatment. Importantly, an epilepsy syndrome does not necessarily align one-to-one with an etiological diagnosis but serves a distinct purpose in guiding treatment and management (3) (Figure 6).

Finally, as a summary the diagnosing epilepsy necessitates a comprehensive evaluation that includes a detailed medical history, physical examination, neuroimaging (e.g., MRI, CT), and EEG recordings. Additionally, specialized investigations such as video-EEG monitoring, neuropsychological testing, and genetic analysis may be employed to ascertain the diagnosis and identify potential comorbidities.

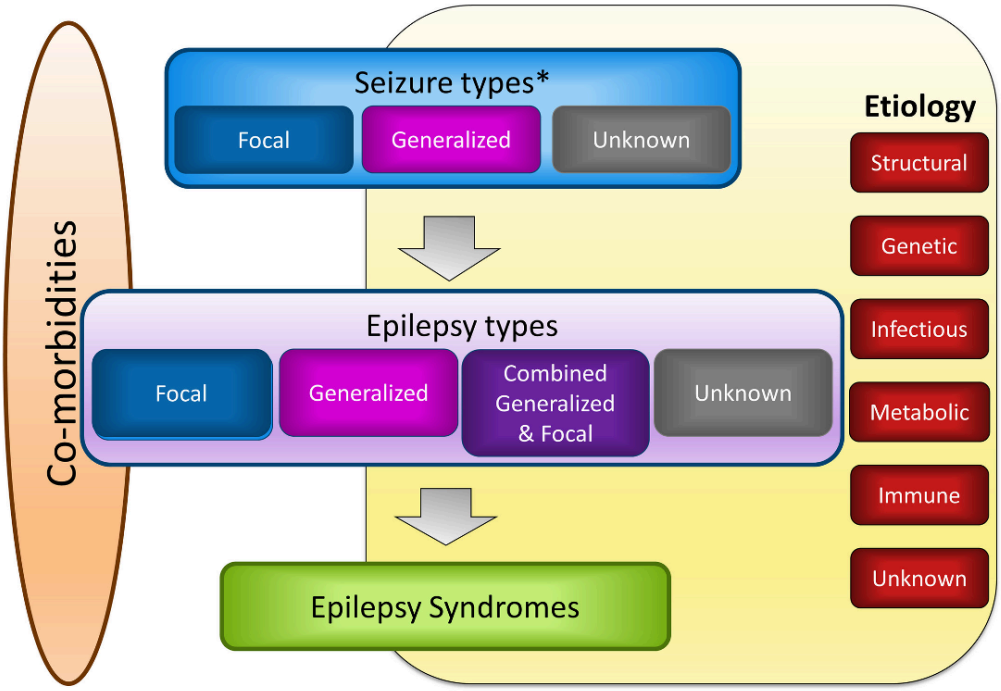


Figure 6. ILAE 2017 classification of the epilepsies. From Scheffer et al. (2017) (6)

1.1.2.Treatment

To address the general aspects of epilepsy treatment in this dissertation, therapeutic options for patients have been divided into two groups: for patients without Drug-Resistant Epilepsy and for patients with Drug-Resistant Epilepsy. Before continuing, it is important to define this concept.

Drug-resistant epilepsy, also known as pharmacoresistant epilepsy, is defined by the ILAE as the failure to achieve seizure freedom with at least two appropriately chosen antiseizure drugs (ASDs), given in adequate doses for a sufficient period of time, with no major side effects [39, 40]. Drug resistance is not simply determined by the number of ASDs used, but rather by the effectiveness of treatment in achieving seizure control (48).

. This concept is crucial for guiding therapeutic decisions, as it indicates that alternative treatment options (49)

Traditionally, the mainstay of epilepsy treatment has been anti-seizure drugs (ASDs). However, for patients without drug-resistant epilepsy, a well-structured treatment plan can often lead to excellent seizure control and improved quality of life through appropriate ASD selection, dosage adjustment, and strict medication adherence (50,51).

Therapeutic options for patients without Drug-Resistant Epilepsy

Antiseizure Drugs (ASDs): ASDs remain the first-line treatment for epilepsy. For patients without drug-resistant epilepsy, selecting the appropriate ASD, adjusting dosages, and ensuring strict medication adherence often result in excellent seizure control and improved quality of life (52,53). Table 3 provides a summary of various antiseizure drugs (ASDs) based on their generation and primary indications, whereas Figure 7 schematically illustrates the mechanism of action of each ASD.

Table 3. Antiseizure Drugs. From Johannessen et. al (2022) (54).

Older drugs/first generation	Newer drugs/second generation	Newest drugs/third generation
Bromide (BRM)	Felbamate (FBM)	Brivaracetam (BRV)
Carbamazepine (CBZ)	Gabapentin (GBP)[g]	Cannabidiol[a] (CBD)
Clonazepam (CNP)	Lamotrigine (LTG)	Cenobamate (CNB)
Clobazam (CLB)	Levetiracetam (LEV)	Eslicarbazepine (ESL)
Ethosuximide[e] (ESM)	Oxcarbazepine (OXC)	Everolimus[b] (EVR)
Phenobarbital (PB)	Pregabalin (PGB)[g]	Fenfluramine[a] (FNF)
Phenytoin (PHT)	Tiagabine (TGB)	Ganaxolone[a] (GNX)
Primidone (PRM)	Topiramate (TPM)	Lacosamide (LCM)
Sulthiame[f] (SLT)	Vigabatrin[d] (VGB)	Perampanel (PMP)
Valproic acid (VPA)	Zonisamide (ZNS)	(Retigabine)[c] (RTG)
		Rufinamide[a] (RFM)
		Stiripentol[a] (STM)

Note: Classification of the ASMs used for prophylactic treatment, according to the time of approval, from the 1850s for bromide, to fenfluramine in 2021 was based on previous reviews, see.[3,10,11] Abbreviations in parentheses.

[a]Orphan drugs, specific indications in one or more of the following; Dravet syndrome, Lennox Gastaut syndrome or epilepsy associated with tuberous sclerosis complex (TSC), CDKL5-related epilepsy (*cyclin-dependent kinase-like 5) deficiency disorder*.

[b]Indication in tuberous sclerosis complex only.

[c]Withdrawn from the marked due to adverse effects.

[d]Limited use in infantile spasms due to visual field restriction.

[e]Used in absence epilepsies, primarily in children/adolescents.

[f]Used in benign childhood epilepsies in some countries. In addition to these drugs, steroids were also mentioned, as treatment in specific immune-related epilepsies.

[g]Gabapentin and pregabalin are now considered as N02A, Other analgesics, from 2023, according to the whocc.no/atc_ddd_index.

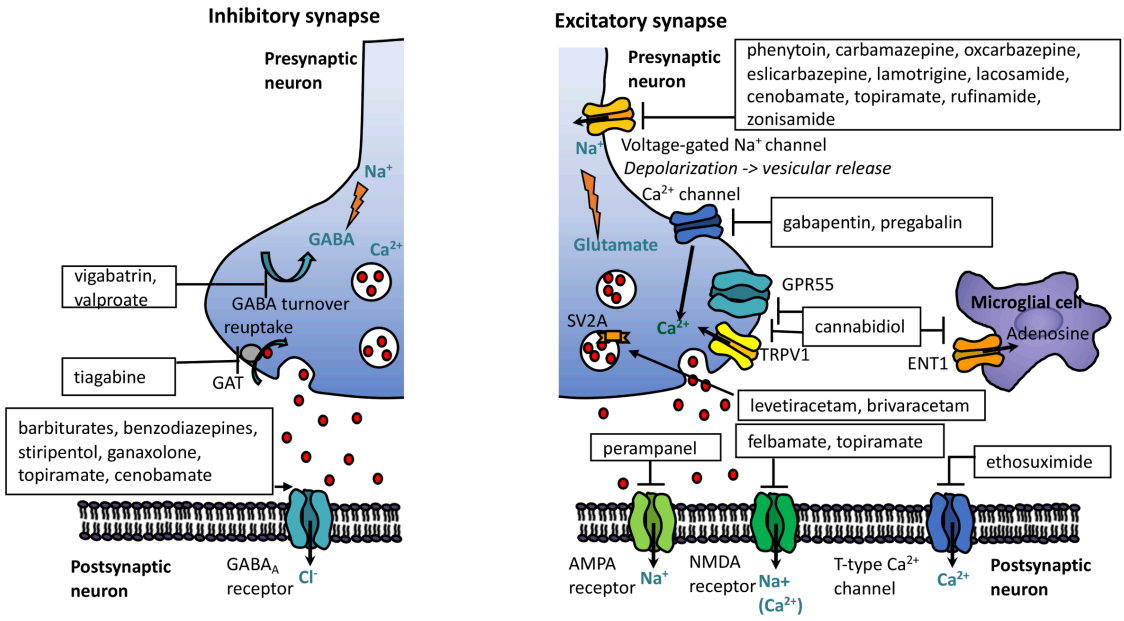


Figure 7. Pharmacodynamic features of antiseizure medications with their main proposed mechanisms of action. Left, inhibitory synapse; right, excitatory synapse. AMPA, α- amino- 3- hydroxy- 5- methyl- 4- isoxazolepropionic acid; ENT, equilibrative nucleoside transporter; GABA, gamma amino- butyric acid; GAT, GABA transporter; NMDA, N- methyl- D- aspartate; GPR55, G protein- coupled receptor- 55; TRPV, transient receptor potential vanilloid. The mechanisms of action of fenfluramine and everolimus are not shown. The figure is based on. From Johannessen et. al (2022) (54).

Beyond the utilization of ASDs, there exist fundamental cornerstones in the management of epilepsy, as delineated below:

Lifestyle modifications: Some lifestyle changes, such as maintaining regular sleep patterns, managing stress, and avoiding seizure triggers, can significantly reduce seizure frequency. (55,56).

Ketogenic diet: A high-fat, low-carbohydrate dietary approach that mimics the metabolic state of fasting, offers benefits in reducing seizures.(57–60).

Non-invasive neuromodulation: Non-invasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have shown promise in reducing seizure frequency in some patients. (61).

Emerging therapies for Drug-Resistant Epilepsy

For patients with drug-resistant epilepsy, where pharmacological treatment alone is insufficient, innovative therapeutic strategies come into play:

Responsive Neurostimulation (RNS): RNS involves the implantation of a device in the brain to detect aberrant electrical activity and deliver precise electrical stimulation to mitigate imminent seizures (50). Clinical evidence indicates that RNS offers substantial reductions in seizure frequency, particularly benefiting patients with focal drug-resistant epilepsy (62).

Vagus Nerve Stimulation (VNS): VNS is another neuromodulation technique involving surgical implantation of a device to stimulate the vagus nerve, reducing seizure frequency and severity (63). Recent advances in VNS technology have improved its therapeutic efficacy, making it a valuable alternative for specific patient cohorts (64).

Deep Brain Stimulation (DBS): DBS involves the implantation of electrodes in specific brain regions, administering controlled electrical impulses to influence brain regions implicated in seizure onset (65). While its clinical application is still under investigation, DBS shows promise for managing drug-resistant epilepsy under specific circumstances (66,67).

Epilepsy surgery: Epilepsy surgery has evolved as a transformative therapeutic option for carefully selected patients (68). Surgical procedures aim to remove or disconnect epileptogenic brain tissue responsible for seizure generation (69). Techniques such as resective surgery, callosotomy, stereotactic radiosurgery, laser interstitial thermal therapy (LITT), and responsive neurostimulation have shown remarkable success in achieving seizure freedom or significantly reducing seizure burden (68,69).

Cannabidiol (CBD): CBD, a non-psychoactive compound derived from the cannabis plant, has garnered attention for its potential anticonvulsant properties (70). Its interactions with the endocannabinoid system contribute to reducing neuronal excitability, proving effective in specific epilepsy syndromes (70).

Gene Therapies: The burgeoning field of gene therapy focuses on genetic modifications associated with epilepsy, aiming to restore normal cellular function and halt seizure progression (71). Preclinical studies offer promises, and clinical trials are actively exploring specific genetic epilepsy subtypes (72).

Optogenetics: Optogenetics involves the manipulation of neuronal circuits through light-sensitive proteins, offering precise control for epilepsy research (73). This methodology has provided profound insights into neuronal dynamics, identified seizure-prone regions, and elucidated the role of specific neuronal cell types (73–75).

After an overview of the general aspects concerning epilepsy diagnosis and management, our focus now shifts to a more specific entity: mesial temporal lobe epilepsy (mTLE).

1.2. Mesial Temporal Lobe Epilepsy (mTLE)

Mesial temporal lobe epilepsy is a complex neurological condition that warrants a comprehensive examination due to its high prevalence and significant impact on patients' lives. Characterized by recurrent complex partial seizures, mTLE often becomes drug-resistant, affecting approximately 30% of individuals diagnosed with this condition (76). Understanding mTLE involves delving into various aspects, from clinical presentation and EEG patterns to the histopathological features of the condition.

One of the primary challenges in diagnosing mTLE is recognizing its unique clinical characteristics. Patients with mTLE may experience seizures with distinct semiology, including automatisms and alterations in consciousness (77,78). These clinical features often point to the involvement of the temporal lobe and necessitate further evaluation to confirm the diagnosis. Additionally, the temporal lobe's role in memory and emotion regulation can contribute to the psychosocial aspects of mTLE, impacting patients' overall quality of life (79).

EEG remains a critical tool for diagnosing mTLE, as it can reveal specific patterns associated with temporal lobe seizures (52,53). Interictal spikes and ictal discharges observed on EEG recordings provide valuable insights into the localization of the epileptogenic focus within the temporal lobe (81). However, the interpretation of EEG findings requires expertise to distinguish mTLE from other seizure types accurately. Furthermore, a subset of patients may experience atypical seizure semiology, leading to potential misdiagnoses and delays in appropriate treatment (82).

Complementing clinical and EEG assessments, neuroimaging techniques, such as magnetic resonance imaging (MRI), offer critical insights into structural abnormalities within the temporal lobe, particularly the hippocampus (83). In mTLE, hippocampal sclerosis is a frequent finding and serves as a histopathological hallmark of the condition (84). This condition is characterized by severe neuronal loss and gliosis in the hippocampus, contributing to the intractable nature of seizures (84,85). However, the exact etiology of hippocampal sclerosis remains an active area of research.

For individuals facing drug-resistant mTLE, surgical intervention may represent a promising therapeutic avenue. Anterior temporal lobectomy (ATL), a well-established surgical procedure, involves the removal of the anterior temporal lobe, including the hippocampus. The goal of ATL is to disrupt the epileptogenic network responsible for seizures (86). Nevertheless, the decision to undergo ATL is multifaceted and requires careful consideration of potential benefits, such as improved seizure control, and potential risks, including postoperative cognitive deficits and language disturbances (86,87).

In conclusion, mTLE presents a multifaceted clinical challenge that necessitates a holistic diagnostic approach. The amalgamation of clinical, EEG, neuroimaging, and histopathological findings facilitates the accurate diagnosis. For patients grappling with drug-resistant mTLE, ATL emerges as a viable therapeutic option, albeit one that demands meticulous evaluation and counseling to optimize patient outcomes.

Nevertheless, it is essential to consider that adherence to the diagnostic algorithm recommended by the ILAE underscores the significance of identifying etiology. This is pivotal due to its prognostic and therapeutic ramifications for patients. In this context,

addressing mesial temporal lobe epilepsy stemming from hippocampal sclerosis assumes paramount importance.

1.3. Mesial Temporal Lobe Epilepsy with hippocampal sclerosis

Given the intricate details outlined in preceding sections, it might be posited that mesial temporal lobe epilepsy accompanied by hippocampal sclerosis represents a subtype of focal epilepsy encapsulated within the broader classification of mTLE. Yet, the multifaceted nuances intrinsic to its pathology have prompted a contemporary classification proposal including this condition as a distinct syndrome, the nuances of which are explained in the subsequent section (32).

The mesial temporal lobe epilepsy with hippocampal sclerosis (HS) is a complex neurological condition characterized by the pathological changes within the mesial temporal structures, notably the hippocampus (88,89). This condition has garnered significant attention in the field of neurology and epilepsy due to its clinical relevance and intricate underlying mechanisms (88).

Definition and epidemiology: mTLE-HS is primarily defined by the presence of specific histological changes, particularly sclerosis, in the mesial temporal structures, most commonly the hippocampus (88,89). This condition represents a significant proportion of drug-resistant epilepsies and is a leading cause of adult epilepsy worldwide. Its exact prevalence varies across different populations, but it remains a substantial healthcare concern, emphasizing the need for a comprehensive understanding of its pathophysiology and clinical implications (90).

Histological findings: Histopathologically, mTLE-HS is characterized by selective neuronal loss and gliosis in the hippocampal formation, primarily affecting the cornu ammonis (CA) regions, specifically in the CA1, CA4 (48) and the dentate gyrus (88,91,92). This neuronal damage and gliosis contribute to the hallmark hippocampal sclerosis observed in affected individuals (92). While the exact etiology of mTLE-HS remains multifactorial and not completely elucidated, it often occurs as a consequence of diverse insults, including prolonged febrile seizures, head trauma, or other factors (32). While hippocampal sclerosis can be classified into distinct subtypes based on the location and severity of cell loss (93), it is the CA1 segment that is most severely affected in the most common type, with over 80% cell loss (94). Other hippocampal regions, including CA2, CA3, and CA4, also show significant cell loss, although less pronounced than in CA1.

The dentate gyrus (DG) is usually affected by granule cell (93,94). GCD is characterized by an expanded granule cell layer, an ill-defined boundary with the molecular layer, and the presence of ectopic granule cells (93). While GCD is prevalent in TLE cases, its association with clinical outcomes remains unclear (93,94).

The ILAE Task Force has proposed a classification system that distinguishes three types of hippocampal sclerosis based on the dominant region of neuronal cell loss:

HS ILAE type 1: This type exhibits severe neuronal cell loss predominantly in the CA1 and CA4 regions, with a dense network of astrogliosis.

HS ILAE type 2: This type demonstrates primarily CA1 neuronal loss, with minimal cell loss in other regions.

HS ILAE type 3: This type showcases dominant CA4 cell loss, along with significant granule cell loss in the dentate gyrus.

While both CA1 and CA4 are involved in HS type 1, CA1 predominant type 2 and CA4 predominant type 3 have been less systematically studied. Some reports suggest that patients with these rarer types may have a less favorable postsurgical outcome, potentially due to a different epilepsy history (94).

In a small percentage of TLE cases, no significant neuronal loss is observed despite evidence of seizure activity in the mesial temporal lobe (93,94). This condition, characterized by reactive gliosis alone, is referred to as "no hippocampal sclerosis with gliosis only (no-HS)" (95). This finding highlights the complexity of hippocampal damage in TLE and suggests that gliosis, in isolation, might play a role in the pathophysiology of seizure activity (93).

Table 4 provides a summary of the pathological subtypes observed in mTLE-HS (ILAE consensus), while Figure 8 illustrates the histopathologic subtypes of hippocampal sclerosis in patients with TLE.

Table 4. Classification of hippocampal sclerosis (ILAE consensus). From Blumcke et al. (2013) (93).

	Subfield pathology patterns of neuronal cell loss and gliosis (in *en bloc* resected samples)			
Class. [a]	HS ILAE Type 1	HS ILAE Type 2 "CA1 Predominant"	HS ILAE Type 3 "CA4 Predominant"	No-HS / Gliosis only
CA1 [b]	2	1 - 2	0 - 1	0
CA2 [b]	0 - 2	0 - 1	0 - 1	0
CA3 [b]	0 - 2	0 - 1	0 - 1	0
CA4 [b]	2	0 - 1	1 - 2	0
DG [c]	0 - 2	0 - 1	0 - 2	0 - 1

The evaluation system focuses on neuronal cell loss (NeuN staining) and is categorized for regions CA1–CA4 as follows: 0 = no significant neuronal loss or only moderate astrogliosis; 1 = moderate neuronal loss and gliosis (GFAP); 2 = severe neuronal loss (majority of neurons absent) and fibrillary astrogliosis. Arrows indicate the progression of neuronal cell loss, with a predominance in CA1 for ILAE HS type 2 and in CA4 for ILAE HS type 3.

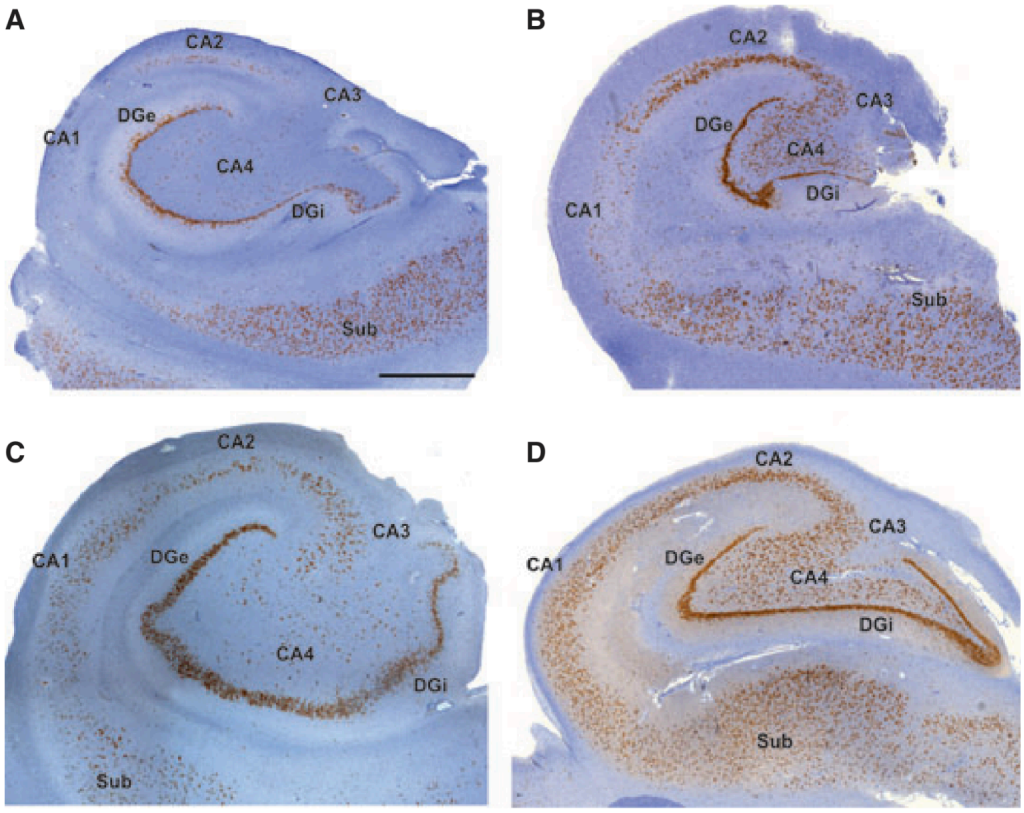


Figure 8. Histopathologic subtypes of hippocampal sclerosis in TLE patients are characterized as follows: **(A) ILAE hippocampal sclerosis type 1** exhibits significant loss of pyramidal cells in the CA4 and CA1 regions. Damage in CA3 and CA2 varies but is often present. The dentate gyrus also shows varying degrees of cell loss, with significant granule cell loss in the internal limb (DGi) in this specimen, and cell preservation in the subiculum (SUB). **(B) ILAE hippocampal sclerosis type 2**, which is less common, shows predominant neuronal cell loss and gliosis in CA1. This pattern is atypical and primarily affects CA1, with minimal damage visible in other regions (Table 1). **(C) ILAE hippocampal sclerosis type 3** features cell loss mainly confined to CA4. This specimen, from a patient with limbic encephalitis and late-onset TLE, demonstrates this subtype. **(D) No hippocampal sclerosis, only gliosis:** Microscopic examination reveals no significant cell loss in any hippocampal subregion (no-HS). All images are NeuN immunohistochemistry with hematoxylin counterstaining on 4-µm–thick paraffin-embedded sections. DGe/DGI, external/internal limbs of dentate gyrus; Sub, subiculum. Scale bar in A = 1,000 µm (applies also to B–D). From Blumcke et al. (2013) (93).

1.3.1. Neuroimaging findings in mTLE-UHS

In the comprehensive understanding of mTLE-HS, neuroimaging studies have played an important role in elucidating the multifaceted structural and functional brain changes

associated with this condition. The integration of various neuroimaging modalities findings reveals the intricate details of the brain alterations characteristic of mTLE-HS.

1.3.1.1. Structural Magnetic Resonance Imaging (MRI)

Structural MRI has been instrumental in unraveling the complex structural changes associated with mTLE-UHS (96). This technique utilizes strong magnetic fields and radio waves to generate detailed images of brain tissue, allowing researchers to visualize anatomical alterations in both gray and white matter (97). Structural MRI is particularly valuable in mTLE-HS as it provides a non-invasive way to identify and quantify the extent of hippocampal atrophy and sclerosis, often serving as a cornerstone for surgical planning and outcome prediction (98,99) (Figure 9).

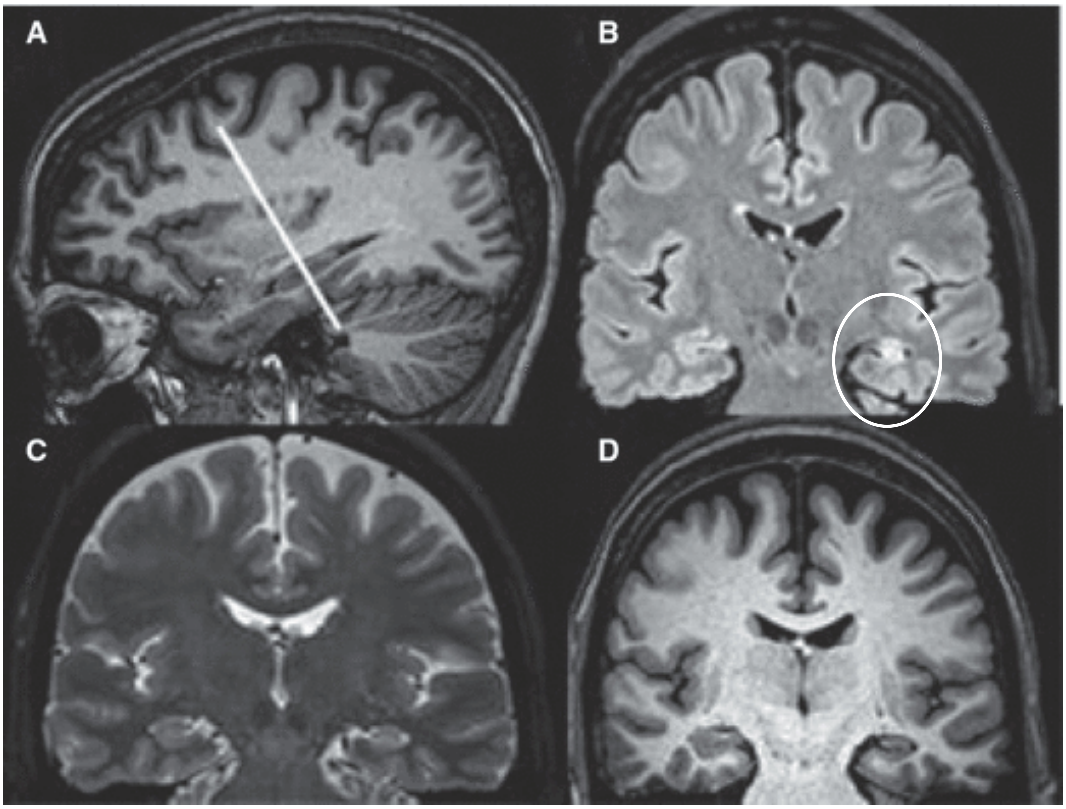


Figure 9. Left hippocampal sclerosis at MRI. **(A)** Sagittal T1 image showing a line that indicates the orientation of the coronal images, which are perpendicular to the hippocampus's long axis and correspond to the coronal T1 level in D. **(B)** Coronal FLAIR image depicting atrophy and increased T2 signal. **(C)** Coronal T2 image corroborating the FLAIR findings. **(D)** T1-weighted coronal image. From Malmgren &. Thom (2004) (100).

A) Gray matter changes

Structural changes in gray matter volume: Gray matter, which encompasses neuronal cell bodies, synapses, and glial cells, is essential for various cognitive and motor functions. The disruption of gray matter integrity and volume in mTLE-UHS can lead to cognitive and behavioral impairments (101), highlighting the importance of studying these changes. In that sense, structural MRI has revealed a consistent pattern of hippocampal atrophy in mTLE-HS patients, characterized by a reduction in hippocampal volume (98). This atrophy is frequently observed in the ipsilateral hippocampus, meaning the hippocampus on the same side as the epileptogenic focus (10). Studies have shown a significant correlation between hippocampal volume reduction and the severity of epilepsy, suggesting that atrophy may be also a consequence of the disease progression (98,102).

Studies utilizing voxel-based morphometry (VBM) have provided further insights into the extent and patterns of gray matter volume (GMV) reductions in mTLE-HS (98,103,104) (Figure 10).

Also, a meta-analysis of VBM studies in patients with mTLE-UHS revealed consistent GMV reductions in specific brain regions. Compared to healthy controls, MTLE-HS patients demonstrated significant GMV decreases in the parahippocampal gyrus (105–107), left pulvinar (98,108), and right pyramid (107). Further analysis revealed distinct

patterns of GMV reduction between subtypes. The left parahippocampal gyrus exhibited the most consistent GMV decrease in patients with left-sided mTLE-HS (LmTLE-HS), while the right parahippocampal gyrus showed the most consistent reduction in patients with right-sided mTLE-HS (RmTLE-HS). No shared regions of significant GMV reduction were observed between LmTLE-HS and RmTLE-HS. These findings suggest that mTLE-HS patients experience significant GMV reductions beyond the hippocampus, and that these reductions differ between subtypes. These findings, if replicated with larger sample sizes, could have implications for the clinical diagnosis of mTLE-HS (109).

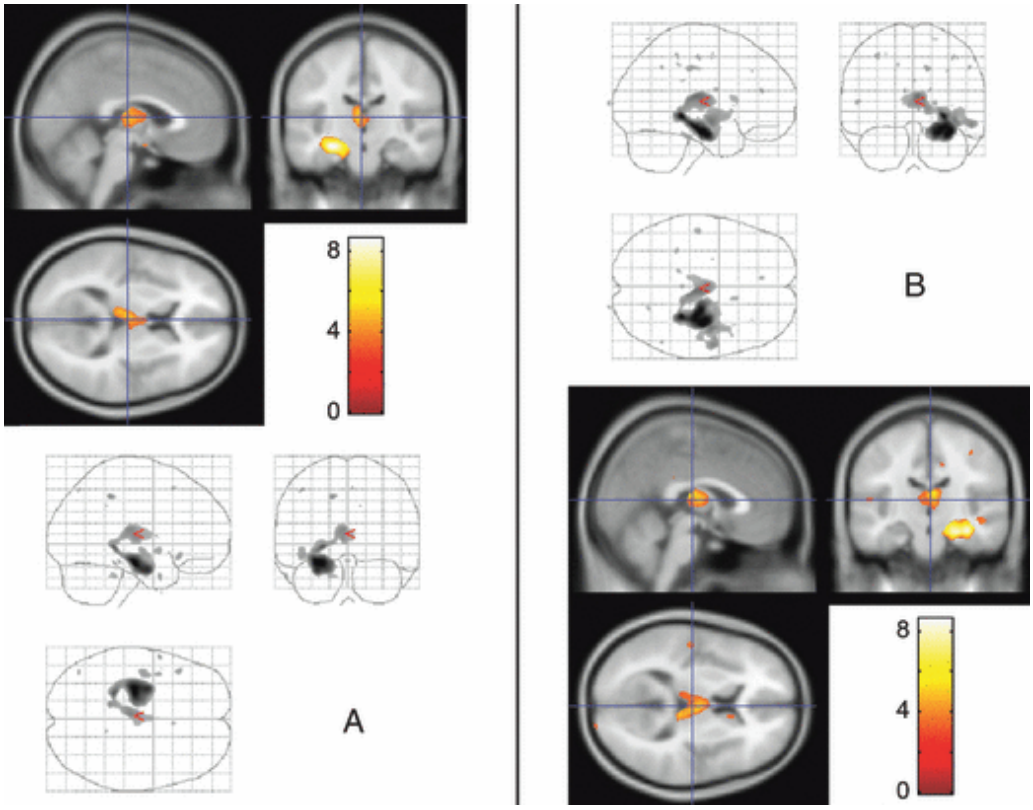


Figure 10. Alterations in gray matter volume (GMV). **(A)** Decrease in GMV is observed in left-sided mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE/HS) when compared to healthy individuals. **(B)** Decrease in GMV is also noted in right-sided MTLE/HS in contrast to healthy individuals. Both visual representations have been adjusted for a false discovery rate (FDR) with a significance level of $p < 0.05$. From Pail et al, (2010) (98).

Hippocampal subfields alterations: The hippocampus, a critical brain structure for learning and memory, is composed of distinct subfields with specialized functions (110–112). Further analysis using advanced segmentation techniques allows for the visualization and quantification of specific hippocampal subfields, such as the dentate gyrus, CA1-CA4, and subiculum (113,114). High-resolution MRI studies have revealed specific patterns of atrophy in hippocampal subfields highlighting the heterogeneity of hippocampal changes in mTLE-HS (115). For instance, it has been demonstrated that the dentate gyrus is particularly susceptible to atrophy in mTLE-HS. The CA1 region and the subiculum, a region that connects the hippocampus to other brain regions, are also prone to atrophy in patients with mTLE-HS (116,117).

Cortical thickness: Neuroimaging studies have consistently demonstrated that mTLE-UHS is associated with significant alterations in cortical thickness (118–120), even in pediatric populations (121). Particularly in children suffering mTLE-HS the alterations were found mainly in the frontal, parietal, and temporal regions. In patients with left side lesion, cortical thinning was found in the ipsilateral caudal middle frontal gyrus, accompanied by increased thickness in the contralateral inferior temporal gyrus. Patients with right lesion exhibited a more widespread pattern of cortical thinning in the posterior parietal, posterior frontal, and occipital regions, both ipsilateral and contralateral to the affected hippocampus. These findings suggest a complex and asymmetric impact of mTLE-HS on brain structure (121).

In adults, a recent study utilizing a fully Bayesian spectral method, which accounts for the complex spatial structure of MRI data, has provided further insights into cortical thickness alterations in mTLE. This study found that left mTLE patients exhibited cortical thinning in bilateral caudal anterior cingulate, lateral orbitofrontal (ipsilateral), the

bilateral rostral anterior cingulate, frontal pole and temporal pole (ipsilateral), caudal middle frontal and rostral middle frontal (contralateral side), while right TLE patients showed thinning only in the entorhinal area (ipsilateral) (122). Regarding the relation of cortical thickness and epilepsy surgery the investigation of Li and colleagues demonstrated that pre-surgically, patients with mTLE exhibited cortical thinning in various regions, including the ipsilateral entorhinal cortex, parahippocampal gyrus, inferior parietal cortex, lateral occipital cortex, and contralateral pericalcarine cortex, as well as bilateral caudal middle frontal gyrus, paracentral lobule, precentral gyrus, and superior parietal cortex. Conversely, the contralateral rostral anterior cingulate cortex showed cortical thickening. Post-surgically, cortical thinning was observed in the ipsilateral temporal lobe, fusiform gyrus, caudal anterior cingulate cortex, lingual gyrus, and insula. However, the ipsilateral caudal middle frontal gyrus, contralateral pericalcarine cortex, and contralateral precentral gyrus showed significant cortical thickening post-surgically. Notably, the contralateral rostral anterior cingulate cortex exhibited thickening at 3 months but thinned significantly at 24 months (118). These changes, observed both ipsilateral and contralateral to the affected hippocampus, suggest that the epileptic process extends beyond the hippocampus, impacting a wider network of brain regions.

Voxel-Based Morphometry : Is a technique for analyzing brain volume across the entire brain (123,124), which has been used to investigate gray matter changes in mTLE-HS (125). VBM studies have consistently revealed widespread gray matter reductions in patients with mTLE-UHS extending beyond the hippocampus to other brain regions (98,109,126–129). A meta-analysis by Barron and colleagues identified significant gray matter reductions in the thalamus (bilaterally) (130). Furthermore, other VBM study have reported gray matter reductions in the amygdala, entorhinal cortex, parahippocampal

gyrus, and even the cerebellum (131,132) (See the metanalysis performed by Zheng and colleagues (109)).

B) White matter changes

Understanding white matter alterations in mTLE-UHS is crucial for elucidating disease mechanisms, given that matter pathways facilitate communication between different brain regions, and their disruption can lead impairments at different levels. Some of the commonly employed imaging techniques for studying white matter alterations and the main findings in mTLE-UHS are detailed as follow:

Diffusion Tensor Imaging (DTI): DTI is a neuroimaging technique that measures the diffusion of water molecules in white matter (133,134). This allows researchers to assess the integrity and directionality of white matter fibers (135), providing insights into the microstructural changes associated with mTLE-HS (136). DTI studies have consistently demonstrated alterations in white matter microstructure, particularly in the ipsilateral and contralateral temporal lobe (136–142). These studies have revealed a pattern of reduced asymmetry in white matter of mTLE-UHS patients compared to healthy controls, suggesting disruption in white matter tracts (138). In relation with the epilepsy surgery, the study of Li and colleagues examined white matter changes in patients with mTLE who achieved seizure freedom after anterior temporal lobectomy (ATL), revealing dynamic alterations in fractional anisotropy (FA) in both ipsilateral and contralateral brain regions. Initial post-operative changes included a decrease in FA in multiple white matter tracts, likely reflecting surgical disruption. Over time, some regions exhibited an increase in FA, suggesting a potential for structural reorganization and recovery, particularly in the contralateral hemisphere. Conversely, other regions showed continued FA decrease, highlighting ongoing structural changes. The study suggests that the brain

undergoes complex and dynamic structural adaptations following ATL in MTLE patients, showcasing a remarkable capacity for plasticity and functional reorganization in response to surgical intervention (143). Furthermore, a study investigating the default mode network (DMN) in mTLE-UHS patients revealed significant disruptions in both functional and structural connectivity within this network. Using fMRI and DTI, researchers observed decreased functional connectivity between the posterior cingulate cortex (PCC)/precuneus (PCUN) and the bilateral mesial temporal lobes in mTLE-UHS patients compared to healthy controls. Additionally, structural connectivity, assessed through path length and connection density derived from DTI tractography, was also significantly reduced between these regions. Notably, no significant differences were found between the PCC/PCUN and the medial prefrontal cortex (mPFC) in terms of functional or structural connectivity. Further analysis revealed a correlation between functional and structural connectivity in the pathways between the PCC/PCUN and bilateral mesial temporal lobes, suggesting that the decreased functional connectivity within the DMN in mTLE might be a consequence of the reduced structural connectivity underpinning the degeneration of these pathways (144).

Skeletonization: Skeletonization algorithms are used to create a 3D representation of white matter fiber tracts, allowing researchers to assess the integrity and structural changes in these pathways (145). The ENIGMA study has shown a reduced asymmetry in the white matter skeleton in mTLE-HS patients, indicating disruption in white matter tracts compared to healthy controls (146). This large multi-center study, analyzed diffusion-weighted MRI data from a large cohort of epilepsy patients, investigated white matter microstructural differences across various epilepsy syndromes, including mTLE-HS. The study utilized tract-based spatial statistics (TBSS) to derive skeletonized maps of fractional anisotropy (FA) and mean diffusivity (MD), and found that individuals with

TLE-HS exhibited the most pronounced white matter abnormalities, particularly in the ipsilateral parahippocampal cingulum and external capsule. These findings suggest that TLE-HS is associated with significant white matter alterations, highlighting the potential impact of this condition on brain connectivity (146).

Tractography: This technique uses DTI data to reconstruct white matter tracts, allowing for the visualization and quantification of specific pathways connecting different brain regions (147). Tractography helps identify disruptions in white matter connectivity, which can impact communication between brain areas (148,149)**.** Diffusion-based imaging and tractography, techniques have proven valuable for understanding the structural organization of the brain in epilepsy, particularly mTLE-UHS. Studies have shown that tractography can be used to accurately predict and localize epileptogenic lesions, optimizing presurgical planning (150,151). Researchers have identified disruptions in white matter tracts, including the fornix, uncinate fasciculus, and cingulum, in mTLE-UHS patients using tractography (137), suggesting that these alterations may contribute to cognitive and emotional deficits. Furthermore, a study combining magnetoencephalography (MEG) and DTI tractography demonstrated a strong correlation between functional abnormalities quantified by MEG coherence and structural abnormalities in white matter tracts, specifically in the insular cortex, lateral orbitofrontal gyrus, and superior temporal gyrus (152). This suggests that the structural abnormalities in white matter tracts may be linked to the functional interictal activity associated with epilepsy. Recent research has even explored the potential of dynamic tractography for visualizing and localizing interictal spike propagations, offering a unique biomarker for epilepsy (153).

1.3.1.2. Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging, particularly utilizing Blood Oxygen Level Dependent (BOLD) contrast, is a non-invasive neuroimaging technique (154–156). It measures changes in blood flow and oxygenation levels in the brain, reflecting neural activity (155,157,158). When neurons are active, they consume more oxygen, leading to localized changes in blood oxygenation levels. The BOLD signal captures these variations, highlighting areas of increased neural activity in response to specific tasks or stimuli (157).

BOLD fMRI leverages the magnetic properties of blood. Oxygenated and deoxygenated blood have different magnetic susceptibilities, which fMRI can detect (159). This difference creates a contrast in the MRI images, allowing researchers to infer changes in neural activity based on fluctuations in blood oxygenation (159). These changes are mapped onto a three-dimensional model of the brain, providing a spatially accurate representation of active brain regions during various cognitive or behavioral tasks (160). To address the main findings of this technique in mTLE-UHS this section will be divided in fMRI activity and fMRI connectivity.

fMRI Activity

fMRI activity measurements typically focus on identifying brain regions that exhibit increased or decreased activity during specific tasks or in response to stimuli (161–163). This can be used to map brain networks involved in various cognitive processes, such as language, memory, attention, emotional regulation among others (161).

Early fMRI studies in epilepsy focused on identifying regions activated during tasks, such as language or memory retrieval, to help guide surgical planning and minimize cognitive deficits (164,165). For instance, the study developed by Detre and colleagues, found that fMRI provided comparable results to the intracarotid amobarbital test (IAT) for language lateralization, demonstrating its non-invasive potential in presurgical assessment (165). The authors also highlighted the ability of fMRI to precisely localize language function in relation to underlying anatomy, suggesting its potential for tailoring resections to avoid crucial language regions (165). In the context of epilepsy surgery, fMRI activity is also used to assess memory lateralization in patients with TLE. This helps predict the risk of amnestic complications following temporal lobectomy (164,166).

However, fMRI has several limitations when studying epilepsy: **(i)** fMRI's temporal resolution is limited by the relatively slow hemodynamic response, which unfolds over several seconds (167). This makes it less suitable for capturing rapid neuronal events, such as epileptiform discharges (spikes), that occur on a millisecond timescale. The inability to directly study the neural activity during seizures using fMRI poses a significant challenge in understanding these events and their impact on brain function (168). **(ii)** fMRI measures neural activity indirectly through BOLD signals, which can be influenced by various factors beyond neuronal firing, making interpretation less straightforward (169,170). This necessitates careful consideration of potential confounds and requires integration with other neuroimaging modalities, such as EEG, for a more complete understanding (171–173). **(iii)** Distinguishing between increased activation in one condition versus decreased activation in another condition within a task can be challenging (165). This requires careful task design and analysis to avoid misinterpreting the fMRI data (174). **(iii)** Motion, even minor head movements, can severely compromise

the quality of fMRI data (175). This necessitates the use of stringent motion correction algorithms and careful subject positioning during scanning (176,177).

fMRI connectivity

While fMRI activity measurements reveal which brain regions are active, functional connectivity (FC) analyses delve deeper, exploring how different brain regions interact with each other (178). This allows us to investigate the communication and integration within and between brain networks, which is essential for normal brain function (179).

A) Task-based fMRI connectivity

Dynamic brain networks task-based FC analyses often examine how connectivity changes during a specific cognitive task (180,181). This can reveal how networks reconfigure to perform specific functions. One area of interest in epilepsy research is the mentalizing network, which is involved in understanding others' mental states and intentions (180). Studies using functional fMRI have revealed altered patterns of task-related FC in patients with mTLE-UHS, highlighting the complex interplay between brain connectivity, cognitive function, and the epileptic process. For example, the research of Sideman and colleagues has demonstrated that mTLE-UHS patients exhibit a shift in the laterality of brain activation during a scene encoding task (SET), particularly in those with left temporal lobe epilepsy (LTLE), suggesting a potential brain reorganization to compensate for the disruption caused by epilepsy (182). Furthermore, investigations into the role of the hippocampus in visuospatial working memory (WM) have shown that patients with both right and left TLE exhibit distinct patterns of FC within hippocampal networks

(183). These findings emphasize the complex nature of network alterations in mTLE-UHS, with specific patterns of FC disruption potentially varying based on the affected hemisphere. Moreover, studies examining the impact of anti-seizure medications on brain activity have revealed that perampanel, a drug targeting the AMPA receptor, can influence both seizure control and emotional processing. fMRI studies have shown that perampanel can lead to increased activity in the left orbitofrontal cortex (OFC), which is associated with anger and aggression, while also affecting regions involved in seizure control, such as the thalamus and caudate (184). Studies have also examined the mentalizing network, which is involved in understanding the mental states of others, in youth with and without epilepsy. While resting-state connectivity did not differ between groups, youth with epilepsy showed reduced task-based connectivity between the left posterior superior temporal sulcus (pSTS) and bilateral medial prefrontal cortex (mPFC) during facial emotion recognition (185). These findings suggest that epilepsy may disrupt the integration of information within this network during cognitively demanding tasks. These studies underscore the importance of investigating task-related fMRI connectivity in mTLE-UHS to better understand the disease mechanisms and to evaluate the potential impact of treatment interventions on brain function.

B) Resting state fMRI connectivity

Resting-state fMRI connectivity analyzes the intrinsic connectivity patterns of the brain when participants are not performing any specific tasks (186). This allows us to study the brain's default organization and how it might be altered in neurological and psychiatric disorders (187–191). Several studies have revealed that epilepsy disrupts the organization of these resting-state networks (22,192–194), particularly those involved in arousal and

vigilance (195). Specifically, the affected networks in mTLE-UHS Resting-state fMRI studies includes: **(i) Arousal Network:** Research has shown that patients with mTLE-UHS exhibit reduced connectivity between brainstem arousal structures, including the cuneiform/subcuneiform (CSC) nuclei, the pedunculopontine tegmental nucleus (PPN), the ventral tegmental area (VTA), and the frontoparietal-insular neocortex (195–197). This reduced connectivity may contribute to impaired consciousness during seizures and cognitive deficits observed in these patients (196). Interestingly, after successful epilepsy surgery, connectivity between the arousal network and the frontoparietal-insular cortex increased in patients who achieved seizure freedom (196), suggesting a remarkable capacity for functional plasticity in the brain and highlights the potential of surgery to promote the restoration of normal brain connectivity **(ii) Salience Network (SN) and Default Mode Network (DMN):** Further investigations have revealed reduced non-directed functional connectivity within the SN and DMN, as well as between these networks and arousal structures in TLE patients (195,196). Additionally, a loss of top-down influence from the SN to the arousal nuclei was observed, potentially contributing to the cognitive impairments experienced by mTLE-UHS patients. **(iii) Mesial Temporal Structures and Default Mode Network (DMN):** A study examining the connectivity between mesial temporal structures and the DMN revealed that patients with right mTLE demonstrated decreased non-directed connectivity between the right hippocampus and the DMN compared to patients with left mTLE and healthy controls (196). This finding suggests that examining the connectivity between mesial temporal structures and the DMN might be a valuable tool for lateralizing mTLE and for guiding surgical planning. Furthermore, analyses of regional homogeneity (ReHo), a measure of local synchronization in brain activity, have shown increased ReHo in specific regions, such as the parahippocampal gyrus, midbrain, insula, corpus callosum, and sensorimotor

cortex, in mTLE-HS patients, while decreased ReHo was observed in the default mode network (DMN) and cerebellum compared to healthy controls (198). These findings indicate that mTLE-HS is associated with altered patterns of local synchronization in the brain, potentially contributing to seizure genesis and propagation. Several other studies have provided further insights into resting-state connectivity alterations in mTLE-UHS such as: **(i) Hippocampal connectivity:** A study examining the interhemispheric hippocampal connectivity in mTLE using high temporal resolution fMRI revealed a disruption in connectivity initially, followed by a linear increase with disease duration after 10 years. This heightened connectivity seems to result from the hippocampus opposite the epileptogenic focus exerting greater influence over the hippocampus on the same side (199). This suggests that long-term seizure propagation effects may lead to increased interhemispheric hippocampal connectivity; (**ii) Post-surgical changes:** A longitudinal resting-state fMRI study in patients with unilateral mTLE-HS found that even over a short period after surgery, patients presented with bilateral diffuse regional and interregional neural activity alterations. The pattern of these changes differed based on the side of resection, suggesting that surgery can impact brain networks in different ways depending on the location of the intervention (200).

These studies, along with those previously mentioned, highlight the complexity of resting-state brain network alterations in mTLE-UHS. They demonstrate the potential for using resting-state fMRI connectivity as a tool for understanding disease mechanisms, monitoring disease progression, and evaluating the effectiveness of treatment interventions.

Positron Emission Tomography (PET)

Is a neuroimaging technique that uses radioactive tracers to visualize and quantify brain activity (201–203). It's particularly valuable for studying neurotransmitter systems (204,205), receptor binding (206,207), and metabolic processes (208). PET is a valuable neuroimaging technique that provides insights into brain metabolism and receptor binding in patients with epilepsy (96), particularly those with mesial temporal mTLE-UHS. PET studies using fluorodeoxyglucose (FDG) have consistently demonstrated hypometabolism in the hippocampus ipsilateral to the epileptogenic zone in patients with mTLE-UHS (209,210) (Figure 11), reflecting decreased neuronal activity in this region (210). This hypometabolism, which extends beyond the visible lesion on MRI, can also be observed in other brain regions, such as the thalamus, highlighting the broader impact of the epileptic process on brain function. Additionally, PET studies utilizing tracers that bind to specific receptors, like the benzodiazepine receptor, have revealed alterations in receptor binding in mTLE-UHS, suggesting potential changes in neurotransmitter function (211). For instance, a study using the benzodiazepine receptor tracer [11C] flumazenil showed a reduction in receptor binding in the hippocampus and amygdala of patients with mTLE-UHS (212) potentially contributing to seizure susceptibility and cognitive impairments. Importantly, PET findings can be detected even in patients with no visible lesions on MRI, emphasizing the utility of PET in identifying subtle neurological changes associated with epilepsy (213). Overall, PET serves as a crucial tool for understanding the pathophysiology of epilepsy and for guiding treatment decisions.

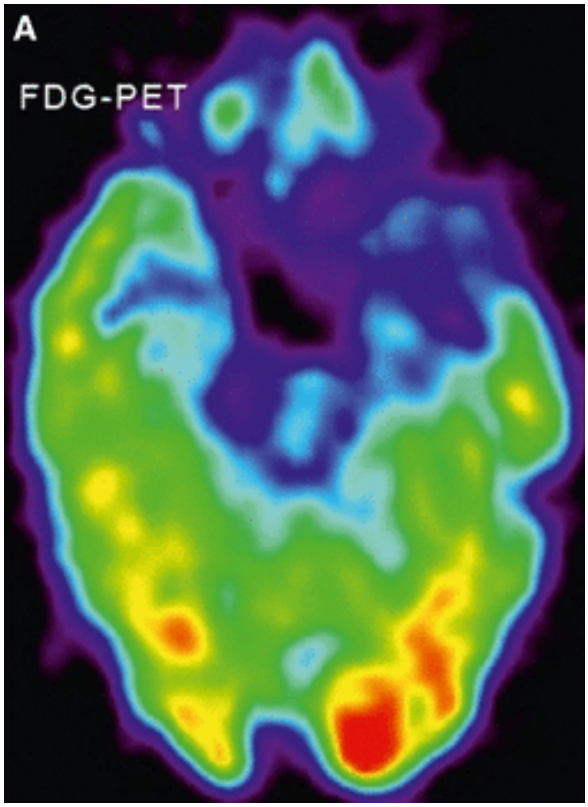


Figure 11. PET findings related to hippocampal sclerosis. **(A)** Axial scan using 18F-FDG PET. While MRI results appeared normal, FDG-PET revealed significant hypometabolism across the left temporal lobe. From Malmgrem & Thom (2012) (100).

Single Photon Emission Computed Tomography (SPECT)

SPECT is particularly useful in evaluating cerebral blood flow and perfusion in real-time. To employed SPECT for mapping ictal perfusion changes in mTLE-HS have contributed to elucidate the hyperactive areas during seizures. The study conducted by Nelissen et al (2006) during ictal episodes revealed marked hypoperfusion in the ipsilateral frontal lobe region. Notably, the ipsilateral temporal lobe displayed the greatest extent of ictal hyperperfusion, juxtaposed with interictal hyperfusion. However, this hypoperfusion in the temporal lobe was relatively less severe when contrasted with the more significant hypoperfusion changes observed in the frontal lobes. These findings elucidate critical aspects of cerebral perfusion alterations in temporal lobe epilepsy, highlighting the

regional specificity and the dynamic interplay between different cerebral areas during ictal and interictal phases (214).

Proton magnetic resonance spectroscopy (1H MRS): Is a non-invasive neuroimaging technique that provides valuable information about the metabolic state of brain tissue (215–217). It measures the concentration of different metabolites, such as N-acetyl aspartate (NAA), creatine (Cr), and choline (Cho), which are associated with neuronal function and integrity (218,219). In patients with mTLE-UHS, 1H MRS studies have consistently shown a reduction in NAA levels, particularly in the hippocampus ipsilateral to the epileptogenic focus (220,221). NAA is a marker of neuronal viability, and its decrease suggests neuronal loss or dysfunction in the affected hippocampus. Additionally, 1H MRS studies have demonstrated reduced NAA levels in the ipsilateral thalamus in mTLE-UHS patients (221,222). These findings suggest that the epileptic process may extend beyond the hippocampus, impacting the thalamus, which is involved in relaying sensory information to the cortex.

The relationship between 1H MRS findings and cognitive function has also been investigated. Studies have shown a correlation between reduced NAA levels in the hippocampus and impaired verbal memory in mTLE-UHS patients (220). Notably, while some studies have found that 1H MRS values may be predictive of postoperative cognitive decline, particularly in verbal memory, further research is needed to confirm these findings (220,222).

While 1H MRS can provide insights into the metabolic changes associated with mTLE-UHS, it is important to note that 1H MRS findings may not always correlate with specific cognitive deficits, and the technique has limitations, such as its susceptibility to partial

volume effects and its inability to capture the dynamic nature of the epileptic process (220,222).

1.3.2. Neurophysiological findings in mTLE-UHS

Electroencephalographical findings: Electroencephalography is a non-invasive neurophysiological technique that records brain electrical activity, is crucial for understanding the complex neurobiological mechanisms underlying mTLE-UHS. EEG recordings provide valuable insights into the location, frequency, and characteristics of epileptic activity, particularly the presence of interictal spikes and the spread of activity during seizures (223–225). Furthermore, EEG, including both scalp and intracranial recordings, can reveal abnormalities in brain activity associated with cognitive processes, such as attention, memory, and language, as well as the potential for functional reorganization after epilepsy surgery (226,227). By examining electrophysiological patterns, researchers aim to better diagnose, monitor, and guide treatment interventions for patients with mTLE-UHS.

Scalp EEG findings in mTLE-UHS: Scalp EEG provides valuable insights into the electrical activity of the brain. It plays a crucial role in diagnosis, monitoring, and guiding treatment decisions.

a. Ictal Findings: Ictal EEG recordings capture the electrical activity of the brain as it undergoes an epileptic episode. **(i) Before surgery:** Ictal EEG recordings, captured during seizures, are essential for identifying the onset and spread of epileptic activity. In mTLE-UHS, ictal EEG typically shows initial temporal delta and delayed theta/alpha pattern within 30 seconds of clinical onset (32,228,229). The presence of these rhythmic patterns in the temporal region, particularly on the side ipsilateral to the epileptogenic

hippocampus, is a hallmark of mTLE-UHS. **(ii) After successful epilepsy surgery**, ictal EEG recordings often demonstrate a significant reduction or absence of ictal activity in the temporal region (32).

b. Interictal findings: Interictal EEG recordings, captured between seizures, often reveal abnormalities that reflect the underlying hyperexcitability of the brain in mTLE-UHS patients. **(i) Before surgery:** The hallmark finding is the presence of interictal spikes in the temporal region ipsilateral to the epileptogenic hippocampus (230,231). These spikes can be sharp waves or spike-and-wave complexes, and they may be present both during wakefulness and sleep. Interictal EEG may also show non-epileptiform regional slowing, particularly in the temporal region (230). This slowing reflects a decrease in neuronal activity and can be an indicator of underlying brain dysfunction. While spikes typically predominate on the ipsilateral side, they may also be present bilaterally, indicating a potential for bilateral involvement or a greater risk of seizure generalization. **(ii) After surgery:** Following surgery, interictal spikes often decrease in frequency and amplitude in the temporal region (232). However, some patients may still exhibit interictal spikes, which might reflect a reorganization of the epileptic network or residual epileptogenic activity.

Intracranial EEG findings in mTLE-UHS: Intracranial EEG (iEEG) involves placing electrodes directly on the brain surface or within brain tissue through surgical procedures. iEEG provides more detailed information about the location and characteristics of epileptic activity than scalp EEG (233).

Ictal Onset Zone: iEEG studies have helped to define the epileptogenic zone (the region where seizures originate) in mTLE-UHS patients with greater accuracy than scalp EEG (234,235). iEEG recordings often reveal high-frequency oscillations (HFOs) and sharp

waves in the epileptogenic hippocampus and amygdala (236). HFOs, particularly those in the fast ripple range (250-500 Hz), are considered highly specific markers of epileptogenic tissue(237).

Spread of Activity: iEEG recordings have also shown that epileptic activity can spread to other brain regions during seizures, potentially explaining the diverse neurological and cognitive symptoms experienced by patients (238–240). These studies highlight the complex nature of epileptic activity and the importance of understanding its spread beyond the primary focus. iEEG can help to identify the extent of seizure activity and to guide surgical planning to ensure that the entire epileptogenic network is resected.

Magnetoencephalography (MEG) Findings in mTLE-UHS: MEG is a non-invasive neuroimaging technique that measures magnetic fields generated by brain activity (241,242). It operates on the principle of the electromagnetic induction, where neuronal currents produce weak magnetic fields that can be detected by highly sensitive sensors called SQUIDs (Superconducting Quantum Interference Devices). MEG provides temporal and spatial information about brain activity with millisecond precision and millimeter-scale spatial resolution. MEG is particularly sensitive to high-frequency activity and can provide detailed information about the location and timing of brain activity (243,244). **Localization of Epileptic Activity:** MEG studies have been used to localize the epileptogenic zone in mTLE-UHS patients, particularly in those with a poor response to antiepileptic medications (245,246) by recording and analyzing the magnetic fields produced during epileptic events, MEG can help identify the focal point of abnormal neuronal activity, aiding in the diagnosis and treatment planning for patients with epilepsy (247–249). Additionally, MEG is valuable for assessing surgical candidacy and monitoring treatment outcomes in epilepsy patients (249). Specifically, in mesial

temporal lobe epilepsy (mTLE), MEG has revealed important insights into the pathophysiology of the condition (250). Studies utilizing MEG have shown aberrant patterns of neuronal activity in the mesial temporal structures, including the hippocampus and surrounding regions (251,252). These findings have enhanced our understanding of the underlying mechanisms of mTLE and have contributed to the refinement of surgical techniques aimed at treating this form of epilepsy (253).

Interictal Activity: MEG studies have also revealed alterations in interictal brain activity in mTLE-UHS patients, suggesting that the epileptic process may disrupt brain function even between seizures (254). Furthermore, MEG studies have shown that changes in MEG coherence, a measure of neural synchronization, correlate with the side of epileptogenicity in patients with mTLE (255). These findings suggest that MEG can provide valuable insights into the functional alterations associated with mTLE-UHS. Overall, MEG serves as a powerful tool in advancing our knowledge of epilepsy and improving patient care through precise localization of epileptogenic regions and characterization of abnormal brain activity.

Event Related Potentials (ERP)

From the available studies on neurophysiological investigations related to mesial Temporal Lobe Epilepsy (mTLE) and Event-related Potentials (ERPs), several key findings emerge. Tian et al. (2023) explored the association between visual episodic memory deficits and physiological measures of memory work load in mTLE patients. They found that impaired episodic memory correlated with increased P200 and decreased P300 amplitudes, with late posterior negativity (LPN) demonstrating sensitivity to left

temporal lobe dysfunction. Moreover, abnormal FN400 and late positive potential (LPC) effects, along with reduced FN400 amplitude, were associated with visual episodic memory deficit in TLE patients (256). Yu et al. (2023) investigated prospective memory impairment in refractory TLE patients and identified inhibition dysfunction as the main cause, evidenced by reduced prospective positivity amplitudes in ERP experiments (257). Lastly, Morange et al. (2023) conducted a systematic review on the use of cognitive evoked potentials, particularly MTL-P300 and AMTL-N400/P600, as markers of the epileptogenic zone in TLE. They found that reduced amplitude of MTL-P300 and AMTL-N400 correlated with high specificity in identifying the epileptogenic zone and predicting postoperative memory impairment, highlighting the potential clinical utility of ERPs in presurgical evaluation and cognitive outcome prediction in TLE patients (258).

Impact on nearby and distant Structures: The pathological changes seen in mTLE-HS extend beyond the hippocampus, impacting adjacent structures within the temporal lobe, such as the entorhinal cortex and amygdala (22,118). Furthermore, emerging research has highlighted the connectivity of the mesial temporal structures with distal brain regions, emphasizing the potential network-wide consequences of mTLE-HS (259). Disruptions in the hippocampal circuitry can lead to aberrant information processing, affecting memory consolidation and emotional regulation (260).

Involvement in reward system and cognitive functions: Recent investigations have shed light on the intricate interplay between mesial temporal structures, including the hippocampus, and the brain's reward system. These interactions have critical implications for various cognitive functions (261). Alterations in this network may contribute to the cognitive impairments and behavioral changes often observed in individuals with mTLE-

HS. Such alterations can manifest as difficulties in decision-making, emotional regulation, and processing of reward-related stimuli (1).

In summary, mTLE-HS represents a complex epileptic condition characterized by specific histopathological changes in the mesial temporal structures, particularly the hippocampus. Beyond its local effects, mTLE-HS can disrupt neural networks, impacting cognitive functions, emotional regulation, and reward processing. Understanding the intricate relationships within this system is crucial for advancing our knowledge of the condition and developing targeted therapeutic strategies.

After detailing the complexities of mTLE-HS and the therapeutic options for patients, including those without drug-resistant epilepsy, we now focus on the specific aspects of this investigation. Considering surgery as a viable therapeutic option for mTLE-HS patients with pharmacoresistance, it is essential to grasp the general aspects of this procedure. This understanding is pivotal in elucidating the specific vulnerabilities of this subset of patients undergoing surgical intervention.

2. Epilepsy surgery in mTLE

Epilepsy surgery provides an opportunity for seizure remission in 30%-40% of focal epilepsy patients unresponsive to anti-seizure drugs. Procedures include resection, stereotactic radiosurgery, corpus callosotomy, and device implantation among others. Candidates undergo rigorous preoperative evaluation to ensure favorable risk-benefit ratios and realistic expectations regarding seizure outcomes and potential risks. Surgical assessment aims to identify the epileptogenic zone and minimize post-operative deficits

through comprehensive evaluation, including imaging assessments, EEG recordings, and neuropsychological evaluation (69) (Figure 12).

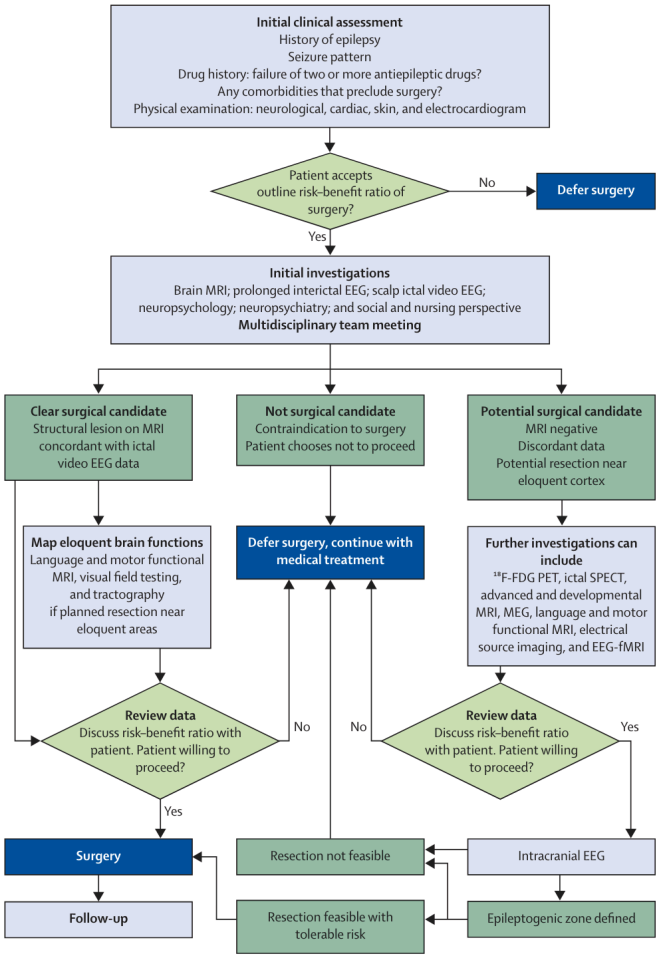


Figure 12. The evaluation routes for epilepsy surgery, illustrating the role of neuroimaging. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. EEG: electroencephalography. MEG: magnetoencephalography. From Duncan et. al (2016) (69).

For patients with mTLE, favorable outcomes are observed when a concordant structural lesion such as hippocampal sclerosis is evident on MRI. Among them, approximately 70% (with a range of 62% to 83%) experience sustained freedom from seizures (86,262).

Currently, the techniques primarily used include resective surgery, stereotactic radiosurgery, and laser interstitial thermal therapy, with the former remaining the

standard (263,264). In resective surgery, the goal is to remove epileptogenic tissue entirely with minimal impact on adjacent structures to mitigate effects on other brain functions (69). The extent of resected tissue may be limited to the hippocampus or extend to nearby structures such as the amygdala and even encompass the anterior temporal pole (265).

Regarding seizure frequency reduction, positive effects have been shown to persist for over 23 years following surgical intervention (266), accompanied by significant and sustained improvement in quality of life (QOL) (267). However, the procedure is not without negative effects or sequelae, which influence patients' satisfaction levels. Commonly reported deficits include visual and mnemonic neurological deficits and cognitive impairments such as verbal and visual memory alterations and naming difficulties (264,268).

Regarding pre-existing psychiatric disorders such as psychosis, anxiety, and depression, numerous studies and meta-analyses have yielded varying results in terms of prevalence rates. Typically, patients may exhibit symptom remission, improvement, exacerbation, or onset following surgery. (269–271).

To enhance our understanding of these findings, especially regarding depression and its central symptom of anhedonia, current models posit dysfunction within the reward system as a significant mediator (272). Considering that epilepsy surgery encompasses mesial temporal structures associated with the reward circuitry, assessing its functionality pre- and post-surgical resection in mTLE-UHS patients could prove advantageous in understanding disease dynamics and treatment efficacy. (27)

2.1. Epilepsy surgery and reward system in mTLE-HS

Current research investigating the association between mTLE-HS and reward processing has predominantly focused on behavioral tasks such as gambling paradigms (21,273,274) and neurophysiological assessments (27). Pre-surgical assessments indicate that individuals with mTLE often demonstrate deficits in decision-making under ambiguity, linked to specific declines in executive function and earlier seizure onset (274). Notably, even in cases of hippocampal sclerosis without amygdala involvement, there is a propensity towards disadvantageous decision-making (21,274). Following surgery, while seizure susceptibility typically remains unchanged, persisting challenges in decision-making under ambiguity underscore enduring cognitive impairments despite intervention (273). However, literature utilizing fMRI remains sparse, with limited studies examining resting-state activity (275,276) and the integration of EEG-fMRI to investigate interictal activity (277).

After outlining the convergence of mTLE-HS, resective surgery, and the reward system, we will now delve into a deeper understanding of this circuit and its associated cognitive processes

3. Reward Processing

Reward processing is a central aspect of cognitive neuroscience and refers to the set of mental operations and brain processes involved in the anticipation, choice, and receipt of rewards. This processing primarily takes place in a collection of brain structures known as the reward system (RS) (278).

The reward system involves the neural mechanisms responsible for recognizing and responding to stimuli that positively reinforce behavior. These rewards can be categorized as primary, such as food and water, or secondary, like money and pleasant smells, with primary rewards inherently valuable for maintaining homeostasis and reproduction. Despite phylogenetic distinctions, both types of rewards engage similar brain regions (279). Furthermore, the reward system not only mediates immediate reward processing but also plays a crucial role in learning and decision-making (280). Through mechanisms such as reinforcement learning, the brain can predict errors and adapt behavior accordingly, as evidenced in conditioning experiments (281,282).

Anatomically and functionally, reward processing involves intricate neural circuits, including one responsible for learning which encode predictions based on stimulus novelty and another responsible for motivation that facilitate the pursuit of stimuli essential for survival (283,284). These circuits integrate inputs from cortical, limbic, and midbrain regions, with the nucleus accumbens serving as a central hub for modulating goal-directed behavior. A well-functioning reward system is vital for adapting to changing or ambiguous environments, where affective responses, associative learning, and memory storage play pivotal roles. Dysfunctional responses to rewarding stimuli have been implicated in various psychiatric disorders and medical conditions, underscoring the clinical significance of understanding reward system dynamics.

3.1. The Reward System

Is an integral component of the brain's neurobiological framework, encompasses key regions like the Ventral Tegmental Area (285,286), Nucleus Accumbens (287–290), and Prefrontal Cortex(291–293), among other more recently described. It's primarily

modulated by dopamine (294–297), a neurotransmitter pivotal for reinforcing behaviors (298,299) and influencing decision-making processes (300–303). This circuit not only drives fundamental survival behaviors by associating actions with pleasure but also plays a significant role in learning through reward-based reinforcement and is responsible for mediating the physiological and cognitive processing of reward (304). Its dysfunction is linked to various psychiatric disorders and addictive behaviors (305), highlighting its critical role in both human behavior and mental health. This intricate interplay of neuroanatomy, neurochemistry, and psychology forms the foundation of our understanding of motivation and decision-making in the human brain.

3.1.1 Neurobiology of the reward system

Over the last few decades, neuroscience has made remarkable strides in unraveling the intricacies of this system, shedding light on its neurobiological basis and its profound implications for cognition, emotion, and behavior.

These lines pretend to delve into the current understanding of the neurobiology of the reward system, drawing upon the latest research findings and breakthroughs in this field.

Dopaminergic pathways: At the heart of the reward system lies the dopaminergic pathway, particularly the mesolimbic dopamine system. Dopamine, a neurotransmitter, is synthesized in the ventral tegmental area (VTA) and projects to several key regions, most notably the nucleus accumbens (NAcc) and the prefrontal cortex (PFC). This pathway is crucial for encoding and reinforcing rewarding experiences (306).

Ventral Tegmental Area (VTA): Anatomically situated in the midbrain, the VTA contains dopaminergic neurons that project to various brain areas. These neurons release dopamine, a vital neurotransmitter, in response to rewarding stimuli (306).

The Nucleus accumbens (NAcc): Situated within the basal forebrain, it integrates signals from different brain regions, assigns motivational significance to stimuli, and promotes reward-seeking behaviors through its D1 and D2 receptors. NAcc has often been considered the "pleasure center" of the brain (306). It integrates signals from various brain regions, including the amygdala and hippocampus, to assign motivational salience to stimuli (307). Recent studies have highlighted the role of D1 and D2 receptors in the NAcc in modulating the perception of reward, with D1 receptors promoting reward-seeking behaviors and D2 receptors suppressing them**.**

The NAcc's role in various impulse behaviors and its interactions with other brain regions like the amygdala and anterior cingulate cortex have been a focus (308). Studies have looked into how inactivation of the NAcc core and shell impacts impulsive behaviors (309).

The Prefrontal Cortex (PFC): Specifically, the ventromedial prefrontal cortex (vmPFC) is vital for reward processing and decision-making processes (293). It evaluates potential rewards and their value, helping individuals make choices that maximize long-term benefits (310). The interaction between the PFC and the NAcc is orchestrated, influencing our capacity to delay gratification and make optimal decisions.

Neurotransmitters and neuromodulators

In addition to dopamine, other neurotransmitters and neuromodulators play pivotal roles in the reward system.

Serotonin: Located throughout the brain, serotonin influences mood regulation and modulates reward-related behaviors, contributing to emotional well-being (311).

Endocannabinoid System: With receptors in the brain, this system also influences reward processing, with endocannabinoids like anandamide and 2-arachidonoylglycerol playing essential roles (311).

The overall dynamics of the reward circuit, including the interactions between these key regions and the role of dopamine, have been the subject of extensive research, shedding light on how the circuit functions in both normal and pathological states (e.g., in addiction and emotional disorders).

4. Reward processing importance

The importance of reward processing is multifaceted, including the following aspects:

M**otivation and learning:** The reward system is deeply involved in motivation since pleasant or beneficial rewards generate the motivation to repeat the actions that produced them being in that manner an essential mechanism of reinforced learning and operant conditioning (290,312).

Decision making: Reward processing influences decision-making capacity by evaluating options with different expected outcomes, including assessing risks and benefits and the ability to delay immediate gratifications in favor of more significant or more lasting rewards (313–315).

Mental health: Dysfunctions in the reward system have been associated with various psychiatric conditions, such as depression, addiction, and schizophrenic spectrum disorders (316–320). For example, in depression, there may be a decrease in sensitivity to rewards (321) , while in addiction, there may be excessive reinforcement associated with certain substances or behaviors (319).

Social development. Reward processing is also crucial in the social context, as positive interactions with others can be seen as rewards that foster cooperation and the relationship's conformation (322).

Survival and well-being: From an evolutionary perspective, reward processing helps ensure survival by reinforcing essential behaviors such as feeding, reproduction, and social interaction (323).

In summary, reward processing is a cornerstone in understanding how humans and other animals assess and act in their environment to maximize positive experiences and survival.

5. Mesial temporal lobe structures and reward system

From the preceding descriptions, the critical intersections between mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-HS) and the reward system become evident. This convergence is informed not solely by the anatomical interconnectedness of mesial

temporal structures such as the hippocampus and the amygdala but also by their extensive links with other neural systems and the associated cognitive processes.

The intricate relationship between mesial temporal lobe structures and other brain structures, systems, and cognitive processes has been meticulously investigated in conditions such as dementia, metabolic disease, and psychiatric disorders (324). Also, this has been evidenced by numerous studies and a meta-analysis scrutinizing the mesial temporal structures connectivity linked to early life adversities (325). The Figure 13 elucidates with remarkable clarity this association, thereby illuminating the potential repercussions of structural or functional disturbances of medial temporal structures over the brain functioning. Extrapolating these findings to mTLE-UHS demonstrates the importance of conducting specific investigations in this population focused on unraveling their vulnerabilities regarding reward processing and other cognitive processes.,

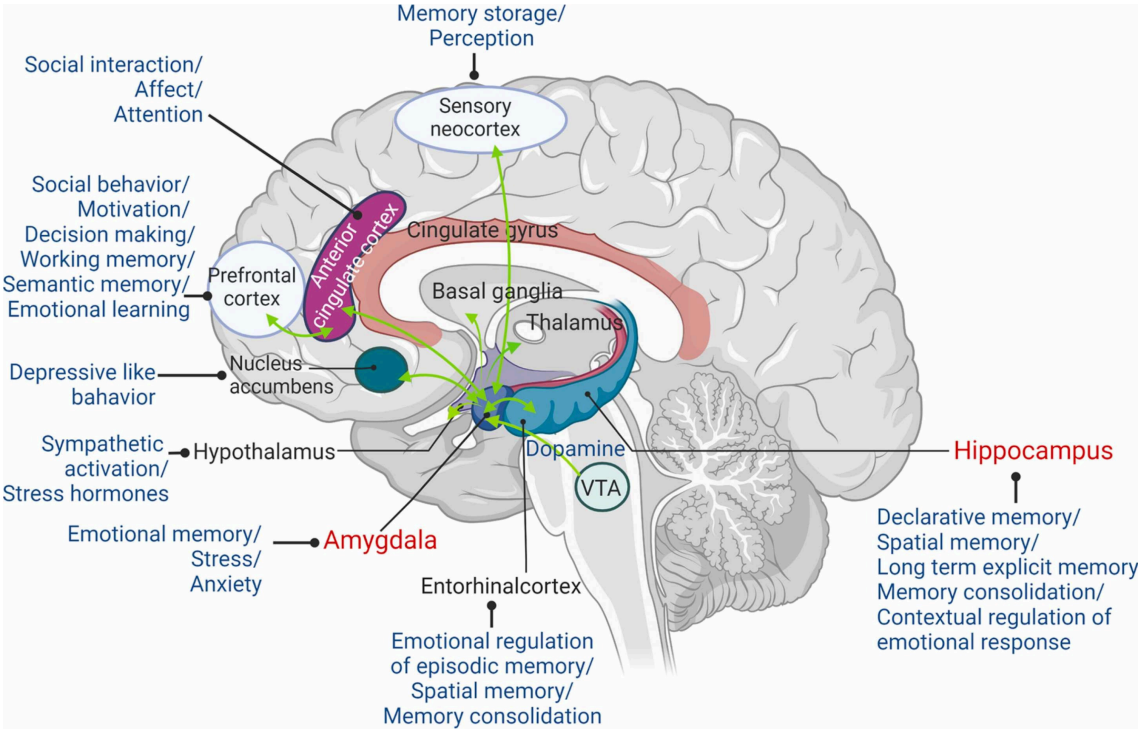


Figure 13. Mesial temporal structure connectivity and associated cognitive processes. From Song (2023) (324).

6. Reward processing approaches

Within the cognitive neurosciences and the general exploration of the human brain, reward processing is a fundamental aspect. Historically, understanding reward began with early behavioral theories, notably those of Ivan Pavlov and B.F. Skinner. These initial forays, rooted in classical and operant conditioning, provided insights into how rewards influence behavior (326).

As neuroscience progressed, the focus shifted to the underlying neural mechanisms. The mid-to-late 20th century saw pivotal developments, particularly in identifying the role of dopamine as a critical neurotransmitter in the brain's reward system (327–329). This period has marked the emergence of neurobiological studies that delved into the functioning of the reward system at a cellular level (330).

The advent of modern neuroscientific techniques, especially functional neuroimaging, brought a more comprehensive understanding of reward processing. Tools like fMRI allowed researchers to visualize and study the brain's reward-related activities in real time, revealing the intricate network of regions involved in reward perception and processing (331). Understanding how reward processing works at the neural level is crucial for comprehending a wide range of human behaviors, including those that are disrupted in disorders like depression, epilepsy, as well as personality disorders like borderline personality disorder (BPD) and behavioral addictions like problem gambling (27,316,332,333).

This section sets the different approaches used for understanding reward processing's complex nature, tracing its historical evolution from basic behavioral concepts to sophisticated neuroscientific models. This journey sheds light on fundamental human behavior and opens avenues for addressing various psychological and neurological disorders.

6.1. Behavioral approach

To understand better the reward processing, one of the elementary approaches is explored how behavior is influenced and shaped by rewards through the use of experimental paradigms.

For investigations conducted in animals, the Skinner box has been used, which allows the observation of how animals modify their behavior in response to rewards and punishments (334–336).

In the case of human studies, various behavioral tasks have been used to understand how rewards influence decision-making and behavior. This exploration has been performed mainly in two scenarios under risk and ambiguity (337–344). When examining reward processing under risk, the focus lies on situations where the probability of different outcomes is known. Individuals can make rational decisions in such contexts by weighing the potential rewards against the associated risks (345). The primary goal is to investigate how people assess and integrate information about the likelihood of various outcomes. Studies under these conditions often employ tasks like probabilistic gambling paradigms, where participants make choices based on known probabilities. Researchers expect that

individuals vary in risk preferences and that brain regions such as the ventral striatum and prefrontal cortex play pivotal roles in computing expected values and making risk-sensitive decisions (346).

Conversely, in conditions of ambiguity, the critical aspect is uncertainty about the probabilities of outcomes (347). These scenarios reflect real-world situations where individuals lack complete information about potential consequences (348). Ambiguity is typically explored using decision tasks with unknown probabilities. Researchers aim to unravel how people deal with the inherent uncertainty, exploring how cognitive processes and neural substrates differ from those observed under risk (339). Findings in these contexts often suggest that people exhibit ambiguity aversion and that different brain regions, including the anterior insula and anterior cingulate cortex, are implicated in processing ambiguous information (347).

Some of the tasks used within scenarios are the following:

Iowa Gambling Task (IGT): The IGT is a popular paradigm to study decision-making under ambiguity and uncertainty (349,350). It involves choosing from different decks of cards, each with varying reward-punishment structures. This task helps in understanding how individuals assess potential gains versus losses over time.

Delayed Discounting Task (DDT): In this task, participants choose between a smaller immediate reward and a larger delayed reward (1,2). This helps in assessing how individuals' value immediate versus future rewards, which is crucial in understanding impulsivity and self-control (351).

Game of Dice Task (GDT): a computer-based decision-making paradigm designed to assess an individual's ability to process rewards and make decisions under explicit risk conditions (352).

Simple Gambling Tasks: These tasks involve making decisions between options with different probabilities and magnitudes of winning or losing (353). They are used to study how individuals process and respond to reward-related information, especially in the context of gambling behaviors (354).

Studies using these tasks have provided insights into various aspects of reward processing, such as the influence of losses on decision-making (355), the role of frequency and temporal proximity of rewards and losses, and the impact of cognitive operations on learning and decision-making processes (356). For instance, the IGT has been pivotal in highlighting the interplay between emotion and cognition in decision-making (357).

These behavioral tasks are vital tools for dissecting the complex nature of reward processing and decision-making, providing valuable insights for both theoretical understanding and practical applications in clinical settings.

These experiments collectively contribute to a deeper understanding of the associative learning processes, where behaviors are reinforced by rewards, elucidating fundamental aspects of motivation and behavioral change.

In addition, these tasks have been used in neuroimaging studies to investigate the neural basis of reward processing. They help in understanding alterations in the reward processing system across different stages of reward processing, from anticipation to outcome appraisal.

In summary, the distinction between risk and ambiguity when examining reward processing allows researchers to uncover the intricacies of human decision-making. Risk studies delve into known probabilities and rational risk-taking behavior, while ambiguity research explores the challenges posed by uncertain situations where individuals must navigate through incomplete information. These complementary approaches contribute to a comprehensive understanding of how the brain evaluates and responds to various facets of reward-related decision-making.

6.2. fMRI approach

In the context of cognitive neuroscience, this technique has been instrumental in studying complex processes like reward processing (331,358–360) , enabling researchers to identify specific brain regions and networks involved in the anticipation , reception, and evaluation of rewards (361–363).

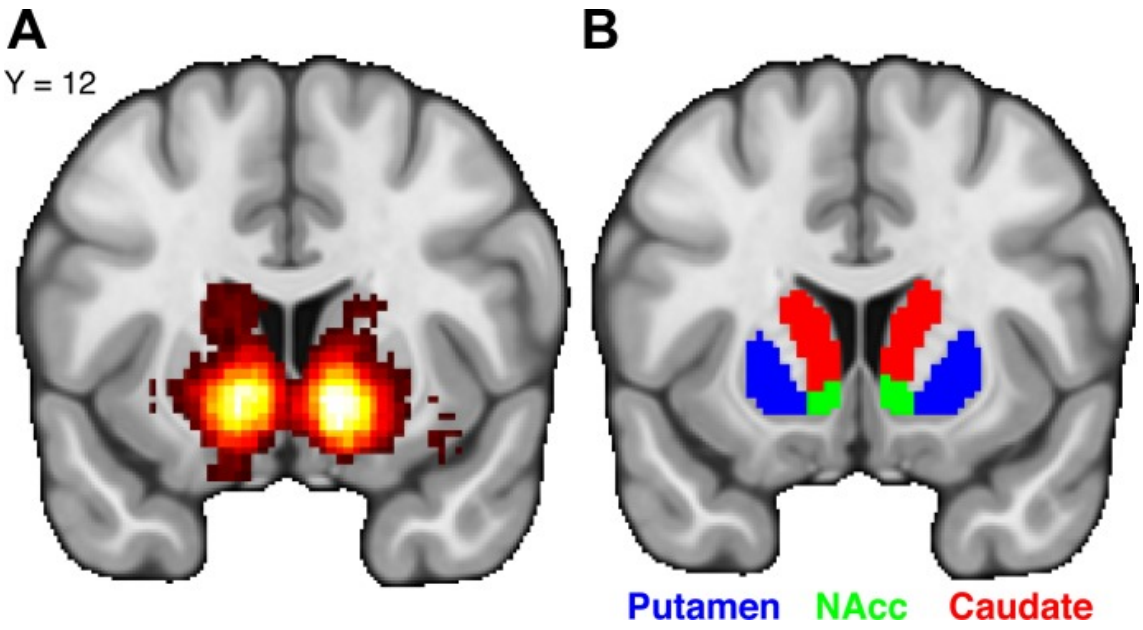


Figure 14. Reward processing and its association with the striatum. **(A)** The result of a meta-analysis of 506 neuroimaging studies highlighted a consistent link between the concept of reward and activation in the striatum. **(B)** Anatomic subdivision of the striatum: putamen (blue), nucleus accumbens (NAcc, green), and caudate (red). From Wang et al. (2016) (331).

In that sense, during the last decades several investigations has being conducted to unravel in the most accurate way the neurobiology immerses in this process, of them the investigation of Smith & Delgado (2016) (331) highlight the most relevant and common aspects across studies as follow: **i)** fMRI has been instrumental in validating seminal findings from animal research within human contexts, effectively mapping the striatum's involvement in reward processing (364–368). This includes the exploration of distinctly human incentives (primary and secondary rewards) and the modulation of behavior within complex social and environmental contexts (369–372). **ii)** The striatal contributions in consummatory behaviors in animal models (373–375) as well as in humans (376–380), and reward-related learning (369,381–384), not only confirming the striatum's critical role in encoding reward signals but also its involvement in behavioral adaptation based on reward feedback, highlighting the differentiation of the striatum's subsections (ventral and dorsal) role across various aspects of reward processing

(326,385–389) Figure 14. **iii)** The application of fMRI to study individual differences and how variations in striatal function correlate with behavioral variability and psychopathology susceptibility (390–392). This approach elucidates the neural underpinnings of interindividual behavioral differences, offering insights into the biological bases of psychopathologies (393,394). **iv)** The importance of brain connectivity and functional integration for refining neural models of reward processing (395). This focus on the striatum's interconnectedness with cortical and subcortical regions and underscores the importance of examining corticostriatal pathways to understand reward processing comprehensively (396,397). An example of the valuable information provided by connectivity studies, is the review conducted by Camara, Rodriguez-Fornells and Münte (2008) (398), where the investigation into neural connectivity patterns revealed that the insular cortex, amygdala, and hippocampus exhibited comparable activation patterns in response to both positive and negative stimuli, as determined by their synchronization with the ventral striatum's activity (398). Notably, the linkage to the amygdala was more significantly highlighted following negative outcomes. Also, an increased connectivity to the medial orbitofrontal cortex was associated with adverse events. The emergence of distinct functional configurations through these analyses underscores the notion that the conventional univariate methodology uncovers the engagement of diverse neural networks in the task at hand, highlighting the multifaceted nature of brain responses to different stimuli. Additionally, it is essential to mention that the development of computational approaches has improved the results derived from connectivity studies, arriving at more accurate information through effective connectivity (399,400). In that sense, the use of advanced statistical technics as well as machine learning in the recent meta-analytic study undertaken by Flannery et. al 2020 (401) embarks on an expansive examination of the neural

underpinnings of reward processing, leveraging a vast compilation of functional neuroimaging data to dissect the multifaceted nature of reward-based decision-making. At the heart of this investigation lies the application of data-driven k-means clustering to categorize 749 experimental contrasts drawn from 176 studies, encompassing the participation of 13,358 healthy individuals. This methodological approach enabled the delineation of seven distinct meta-analytic groupings (MAGs) (Figure 15), each representative of convergent brain activity patterns across a diverse array of reward processing tasks. Two of the identified clusters, MAG-1 and MAG-2, were notably associated with the neural circuits implicated in the encoding of reward prediction errors (RPEs) (364,402,403) a mechanism vital for the adaptive learning of value predictions through both classical and instrumental conditioning paradigms (404). The involvement of the striatum, alongside regions such as the midbrain and ventromedial prefrontal cortex, underscores the critical role of dopaminergic signaling in these processes (364). Further, the distinction between MAG-1 and MAG-2 aligns with the theoretical framework of actor-critic models, suggesting a functional bifurcation between ventral pathways, responsible for updating stimulus values, and dorsal pathways, associated with the valuation of actions (404,405).

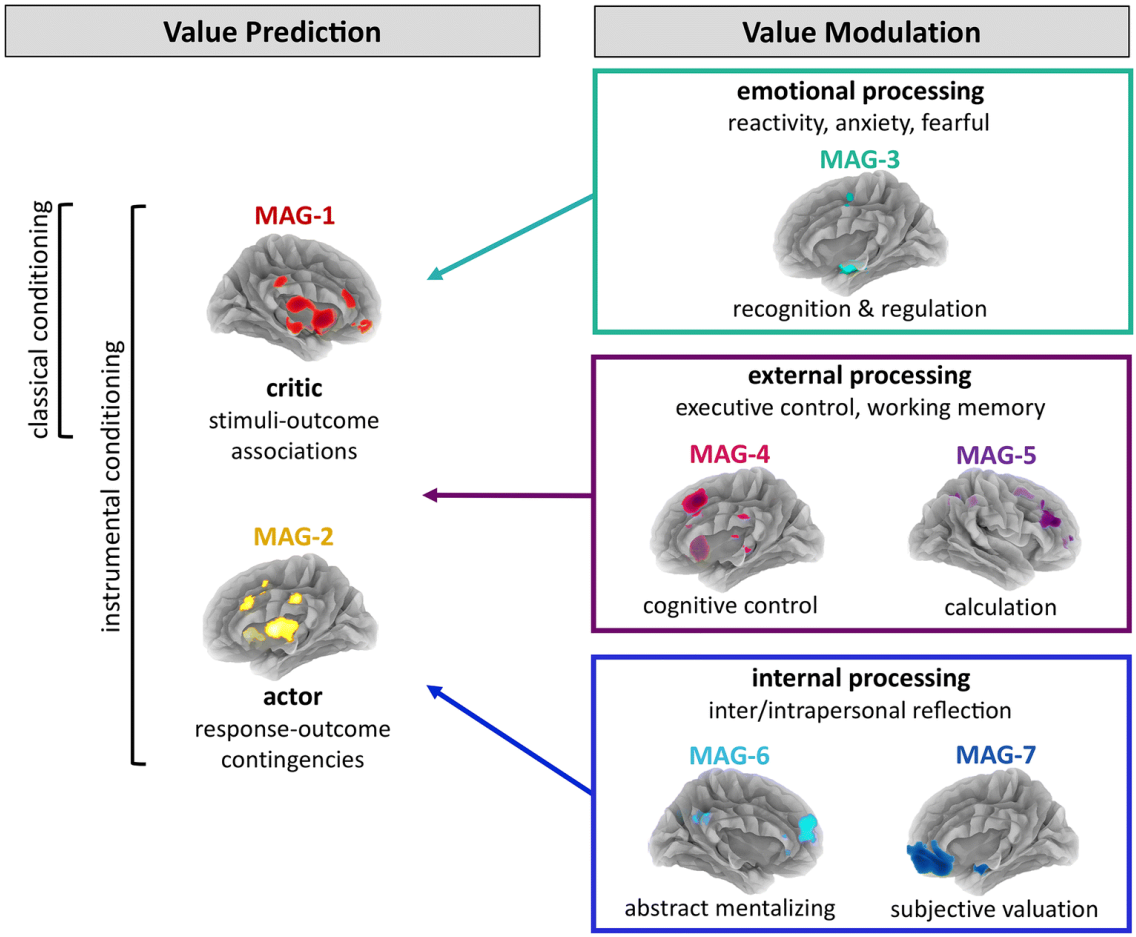


Figure 15. Synthesized Interpretation of Meta-Analytic Groupings (MAGs) Functions: A Heuristic Framework. From Flannery et. al (2019) (401).

The remaining clusters, MAG-3 through MAG-7, shed light on the neural substrates mediating the influence of external and internal factors on reward valuation. These factors range from emotional states and social contexts to cognitive controls such as attention and memory, illustrating the complexity of real-world decision-making scenarios. Particularly, MAG-3's association with the amygdala and hippocampus highlights the impact of affective components on reward processing (293,406,407), while MAG-4 and MAG-5 emphasize the contribution of the executive control network in navigating the probabilistic nature of reward contingencies (408–412).

Delving into the realms of internal states and their influence on reward perception, MAG-6 and MAG-7 provide a nuanced understanding of how personal experiences and affective states sculpt reward valuation. MAG-6, with convergent activity in regions like the central medial prefrontal cortex (cmPFC), reflects self-referential abstract mentalizing (self-referential, mentalizing, mental states, beliefs, moral) (401). This suggests a mechanism through which individual differences in mood, preferences, and past experiences are factored into the computation of reward value, underscoring the personalized nature of reward processing (401) (Figure 16).

Lastly, MAG-7 encapsulates the ventral aspect of the medial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), and subregions such as the amygdala, highlighting a network deeply entwined with the subjective valuation of rewards (413,414).

By integrating these findings within a coherent heuristic framework (401), propose a model wherein emotional, external, and internal influences dynamically interact with RPE signals to modulate outcome valuation. This comprehensive examination offers significant insights into the neural mechanisms of reward processing, emphasizing the diversity of influences that shape our evaluation and pursuit of rewards. This work not only contributes to the theoretical refinement of reward learning models but also holds potential implications for addressing pathological conditions characterized by disrupted reward processing mechanisms.

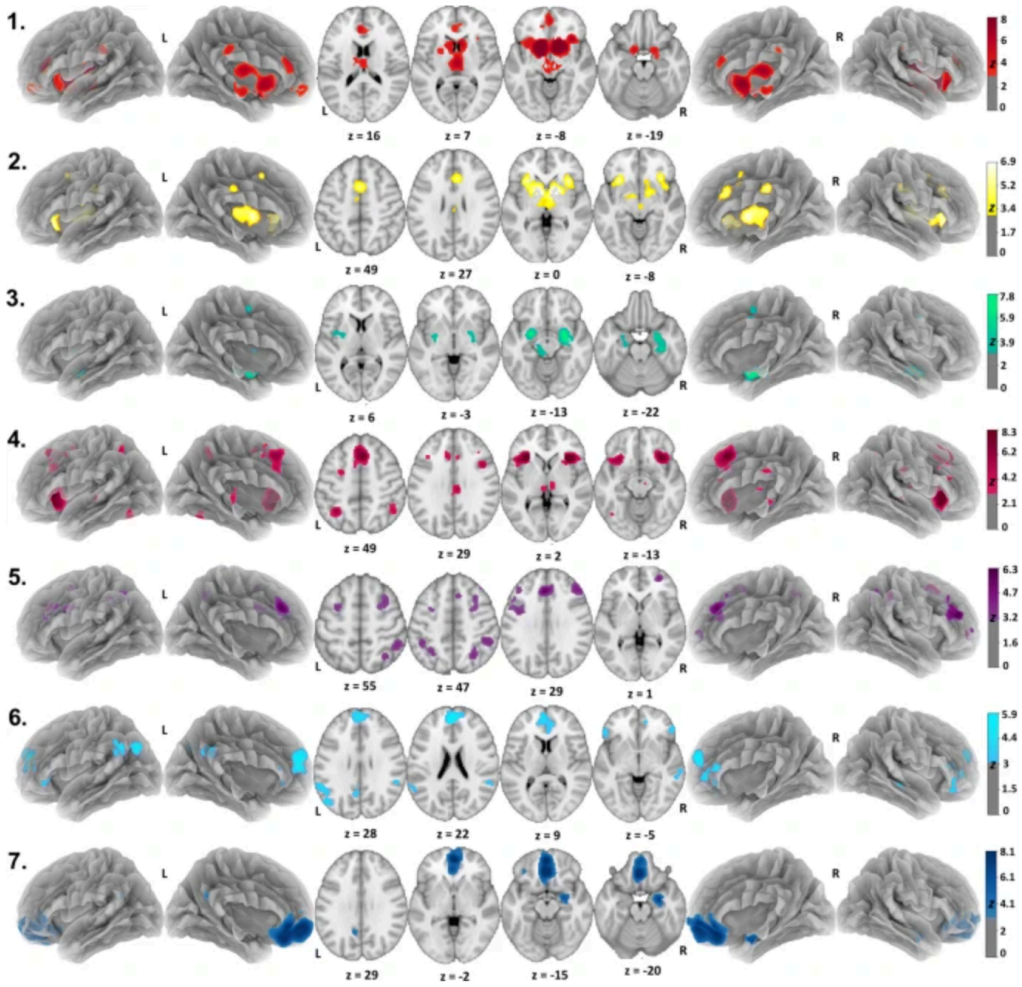


Figure 16. Brain activity profiles associated with each meta-analytic grouping (MAG) of reward processing experiments derived via k-means clustering. ALE images identified significant (pcluster-corrected < .05; pvoxel-level < .001) convergence in dissociable and distributed brain regions across each MAG. From Flannery et. al (2019) (401).

v) The integration of fMRI with other modalities, such as PET and neurophysiological methods, has enriched our understanding of the cellular mechanisms underlying fMRI signals (415–418). This multimodal strategy enhances our understanding of reward processing at a cellular level, promising more accurate interpretations of fMRI data and its implications for reward-related behaviors.

6.3. Electrophysiologic approach

To investigate the intricate workings of reward processing neurophysiologists have employed the electroencephalogram which capture the timing of neural events, providing a high temporal resolution that is ideal for studying rapid brain processes like reward processing (419,420). Within EEG findings the most relevant are:

6.3.1 The Feedback-Related Negativity (FRN)

FRN is an event-related potential (ERP) that emerges about 200-300 milliseconds after feedback is received 7/4/24 9:02:00 PM. The FRN is a negative-going deflection in the EEG signal that is typically larger following negative feedback (e.g., a loss) than following positive feedback (e.g., a gain) (421,422). The FRN is thought to reflect a reward prediction error, indicating the discrepancy between the expected reward and the actual received reward (423,424). This concept aligns with theories of reinforcement learning, which suggest that the brain learns to predict rewards and adjust its behavior based on the discrepancy between predicted and actual outcomes (425). The FRN has been used to investigate a variety of aspects of reward processing, including: **(i) Learning.** The FRN amplitude is often modulated by the magnitude and probability of the reward, reflecting the brain's ongoing learning process (426,427); **(ii) Motivation.** Studies have shown that the FRN amplitude can vary based on the motivational salience of the feedback, indicating how important the reward is to the individual (428,429); **(iii) Decision-Making.** The FRN has been used to assess how the brain evaluates different choices in decision-making tasks, particularly in the context of risky decisions (421,430,431). Research into the FRN has revealed that the timing of feedback can influence the FRN amplitude, with longer delays leading to reduced amplitudes, potentially reflecting a shift from frontostriatal processing to medial temporal involvement (432,433). Individuals with high levels of anticipatory anhedonia, a

symptom of depression, exhibit a blunted FRN response, particularly in the consummatory phase of reward processing, suggesting a disruption in the link between reward anticipation and reward experience (434). Individuals with BPD show reduced FRN amplitudes, suggesting a diminished sensitivity to feedback, particularly negative feedback (435,436). This may contribute to their difficulties in learning from their experiences and adapting their behavior in response to consequences, leading to impulsive and risk-taking behaviors (436).

6.3.2 The P300 and Reward Processing

Another ERP component which appears approximately 300-500ms after a stimulus, has also been implicated in reward processing (437–439). The P300 is thought to reflect a later, more cognitive aspect of reward processing, reflecting attentional allocation and the integration of reward-related information (440,441). Research in problem gambling suggests that the P300 might be particularly sensitive to near misses, those close calls that almost result in a win, but ultimately lead to a loss (442). This finding aligns with the gambler's fallacy, the belief that a losing streak makes a win more likely (443–445). Reduced P300 amplitudes in response to near misses, as seen in problem gamblers, could reflect a diminished ability to recognize and appropriately respond to these potentially discouraging outcomes, contributing to persistent gambling despite negative consequences (445). Additionally, the P300 has been shown to be modulated by the valence, magnitude, and expectancy of rewards (442).

6.3.3. Event-Related Oscillations (EROs)

While the FRN has proven to be a valuable tool for studying reward processing, research has expanded to investigate the role of event-related oscillations (EROs), rhythmic fluctuations in brain activity that occur in response to specific events (446,447). These oscillations, often measured in different frequency bands, are thought to reflect different aspects of brain function, including attention, memory, and cognitive control (448–452).

Delta Band (0.5-4Hz): Delta oscillations are associated with slow-wave sleep, but they can also play a role in cognitive processes, particularly during states of deep concentration or relaxation (453–456). Research suggests that reduced delta activity in response to rewards may be linked to impaired feedback processing, as seen in individuals with mTLE-HS (27). Moreover, research on amphetamine suggests that this stimulant drug increases delta-band power in the human brain, potentially reflecting its effects on the dopamine system and reward sensitivity (457).

Theta Band (4-8Hz): Studies have shown that theta oscillations, particularly in the dorsomedial prefrontal/anterior cingulate cortex (dmPFC/ACC), are involved in processing negative feedback and are reduced in individuals with BPD (446,458). This finding suggests that disruptions in theta oscillations in this brain region might contribute to the difficulties in learning from negative feedback and regulating impulsive behavior seen in BPD (459,460). Genetic factors can also influence these neural rhythms. Research has found that variations in the KCNJ6 gene, which encodes a potassium channel important for neuronal excitability, are associated with differences in theta oscillations during reward processing (461). These genetic variations might contribute to individual differences in reward sensitivity and learning (462). Additionally, individuals at high risk

for alcoholism show lower theta power during reward processing, further highlighting the potential role of theta oscillations in addiction vulnerability (463).

Beta Band (12-30Hz): Beta oscillations are associated with active, engaged states, including focused attention, motor preparation, and cognitive control (464–466). Studies have shown that beta activity is modulated during reward processing, particularly in the hippocampus and ventral striatum (467,468). Increased beta synchrony between these regions has been linked to a heightened reward expectancy, suggesting that the hippocampus may play a role in modulating goal-directed behaviors based on reward anticipation (469–471). Research on gossip suggests that beta oscillations in the reward network might be enhanced during the processing of gossip information, possibly reflecting its arousing and rewarding nature (470).

Gamma Band (30-100Hz): Gamma oscillations are the fastest brain waves and are associated with higher cognitive functions like attention, memory, and conscious perception (472–475). Research in schizophrenia suggests that individuals suffering this condition may show increased gamma activity in the occipital cortex, potentially linked to negative symptoms (476,477). They may also exhibit reduced gamma activity in the frontal regions associated with reward anticipation, suggesting impaired cognitive control (478,479). Additionally, research on insight has revealed that gamma oscillations in the prefrontal cortex are associated with the experience of insight, potentially reflecting a reward-like response to the sudden emergence of a solution (480).

Electrophysiologic approach in mTLE-UHS

In the specific context of mTLE attributed to unilateral hippocampal sclerosis, existing literature underscores the significance of understanding reward-based decision-making processes and their neural correlates. Vilà-Balló et al. (2022) Explored decision-making and electrophysiological feedback processing in patients with mTLE-UHS in comparison to healthy controls. They observed increased risk-taking behavior in decision-making under ambiguity among mTLE-UHS patients, along with alterations in Feedback Related Negativity (FRN) amplitude and delta and theta power.

Notably, no deterioration in behavioral or electrophysiological measures was noted post-surgery. These findings suggest that mTLE-UHS patients exhibit deficits in decision-making under ambiguity, potentially linked to abnormal feedback processing and disruptions in mesial temporal lobe networks. Furthermore, these impairments manifest both pre- and post-surgery, highlighting the need for further research to elucidate underlying mechanisms and therapeutic interventions in this patient population.

6.4. Reward-Processing and Decision-making

Decision-making is a crucial part of human existence. In cognitive neuroscience, its study stands as a testament to the elaborate symphony of neural functions that control our daily lives, with an average individual making over 35,000 choices day-to-day, with each choice being subtly modulated by an array of cerebral structures, including but not limited to the orbitofrontal cortex, ventromedial prefrontal cortex, striatum, cingulate cortex, amygdala, and hippocampus. The mesial temporal portion, particularly the hippocampus and amygdala, is instrumental in maintaining this equilibrium, influencing our survival, adaptation, and the experiential tapestry of pleasure and motivation.

In this context, studying a highly selective group of mTLE-UHS patients before and after epilepsy surgery represents a valuable opportunity to identify potential vulnerabilities within the reward system. This may be accomplished through a synergistic multimodal approach integrating neurophysiological techniques like EEG and neuroimaging (fMRI).

7. Objectives and hypotheses

7.1. General Objective:

To elucidate the impact of pharmacoresistant mesial temporal lobe epilepsy with unilateral hippocampal sclerosis (mTLE-UHS) on reward system functioning, particularly during the valuation phase, and to assess the effects of epilepsy surgery on this process at behavioral, neuropsychological, and neurobiological levels.

7.2. Specific aims and hypotheses:

7.2.1. Study 1: Neurophysiologic correlates of reward processing in mTLE-UHS patients

i) Behavioral level

Objective: To assess decision-making under risk and ambiguity in mTLE-UHS patients before and after surgery using the Iowa Gambling Task (IGT) and the Game of Dice Task (GDT).

Hypothesis: Patients with mTLE-UHS will demonstrate a significantly greater preference for disadvantageous choices in the IGT compared to healthy controls, but not in the GDT.

ii) Neuropsychological/cognitive level

Objective: To assess the cognitive abilities of mTLE-UHS patients in memory and language domains before and after surgery, using established neuropsychological tests.
Hypothesis: Patients with mTLE-UHS will exhibit lower scores in memory and language domains compared to healthy controls.

iii) Neurobiological level

Objective: To investigate the electrophysiological correlates of feedback processing in mTLE-UHS patients during a probabilistic gambling task by analyzing event-related potentials (ERPs) and event-related oscillations (EROs).

Hypothesis: Patients with mTLE-UHS will display abnormal feedback-related electrophysiological activity compared to healthy controls, characterized by alterations in the Feedback Related Negativity (FRN) component and changes in delta and theta power.

iv) Epilepsy surgery effects

Objective: To assess the impact of epilepsy surgery on behavioral, cognitive, and electrophysiological measures of reward processing in mTLE-UHS patients.

Hypothesis: Post-surgery, mTLE-UHS patients will exhibit a worsening of behavioral, cognitive, and electrophysiological impairments in reward processing compared to their pre-surgery performance and healthy controls.

7.2.2. Study 2: Neuroimaging correlates of reward processing in mTLE-UHS patients

i) Behavioral level

Objective:

To determine the extent to which individuals with mTLE-UHS exhibit riskier behavioral patterns and impaired decision-making compared to healthy controls during a probabilistic gambling task, measured by the average of risky choices made.

Hypothesis: Patients with mTLE-UHS will exhibit riskier behavior compared to healthy controls during the probabilistic gambling task, indicating impaired decision-making.

ii) Neurobiological level

Objective: To identify neural correlates of reward processing in mTLE-UHS patients using fMRI during a probabilistic gambling task before and after surgery, focusing on key reward-related brain regions.

Hypothesis: Patients with mTLE-UHS will demonstrate distinct activation patterns in reward-related brain regions compared to healthy controls during both gain and loss conditions.

iii) Epilepsy surgery effects

Objective: To analyze behavioral results and fMRI activation patterns in mTLE-UHS patients during positive and negative feedback processing in the probabilistic gambling task before and after surgery compared to the control group.

Hypothesis: Post-surgically, mTLE-UHS patients will exhibit altered behavioral patterns and distinct brain activation patterns compared to healthy controls, possibly reflecting compensatory mechanisms or neuroplastic reorganization.

8. General Methods and procedures

In the research documented within this doctoral thesis, forty-eight individuals participated, comprising twenty-eight patients with mTLE-UHS and twenty asymptomatic control subjects. The patient cohort, all of whom were receiving outpatient care from the Epilepsy Unit at Bellvitge Hospital in Barcelona, Spain, were identified as suffering from refractory mTLE following comprehensive presurgical assessments at Bellvitge University Hospital and deemed suitable for anterior mesial temporal lobectomy. Diagnostic criteria were met through clinical EEG and MRI, revealing lesions in either the left hemisphere (including fifteen patients, with a female majority of eleven) or the right hemisphere (thirteen patients, including four females). Before and following at least three months postoperatively, each patient was subjected to thorough neurological and neuropsychological evaluations, complemented by continuous video-EEG surveillance.

The surgical interventions, consistently performed by the same neurosurgical team, entailed an en-bloc excision of mesial temporal structures, with subsequent histopathological confirmation of hippocampal sclerosis by uniform pathology criteria. It was ensured that none of the patients experienced a seizure within 24 hours preceding or during the experimental procedures, and all were maintained on a stable regimen of antiseizure medication. The mTLE-UHS cohort was carefully matched to the healthy controls in terms of age, gender distribution, and educational background. The study

protocols were sanctioned by the Ethical Committee of Bellvitge University Hospital (approval PR064/10), and all participants provided informed consent. The control group was assembled via community outreach initiatives. All experimental protocols adhered to the ethical standards outlined in the Declaration of Helsinki.

Within the initial group, seventeen patients with mTLE-UHS and an equivalent number of control subjects completed the neurophysiological evaluations (study 1). In contrast, the entire sample of twenty-eight mTLE-UHS patients and twenty controls underwent the fMRI assessments (study 2).

The variation in participation across the two study components is attributable to disparate technical exigencies.Study 2.

Study 1.

In this study, both mTLE-UHS patients and healthy controls engaged in comprehensive neuropsychological testing. The battery of assessments spanned various cognitive domains, utilizing recognized instruments such as the Wechsler Memory Scale III and Adult Intelligence Scale alongside the Rey Auditory Verbal Learning Test, Trail Making Test, and other established measures. These evaluations facilitated classifying cognitive function into domains like verbal comprehension and working memory. The participants' performance was subsequently summarized and compared pre- and post-operatively for the patient group.

The behavioral component of the study utilized a modified computerized Game of Dice Task (GDT), streamlined from its original version, and the standard Iowa Gambling Task (IGT), which evaluates decision-making under risk. The GDT required participants to predict dice outcomes over multiple rounds, with the IGT focusing on card selections from four decks, each with different risk-reward structures. Participants' accumulated virtual capital served as an ongoing gauge of their performance.

The study also incorporated a probabilistic gambling task designed to prompt choices between two numerical values, with feedback provided on outcomes. The experiment was structured into several blocks, each with a balanced probability of gain or loss, ensuring no bias influenced the decision-making process.

Electroencephalography was continuously recorded during the probabilistic gambling task, focusing on feedback-related potentials and event-related oscillations. Preprocessing of EEG data followed stringent protocols to ensure quality, including re-referencing, artifact rejection, and time-frequency analysis. Statistical analysis of EEG data utilized a repeated-measures ANOVA, examining factors such as evaluation period and participant group, with specific attention to feedback-related negativity and power in frequency bands associated with cognitive processing.

The research adhered to a longitudinal design, with neuropsychological assessments and task-based evaluations occurring before and after surgical intervention for the patient cohort. The study's rigorous methodological approach aimed to unravel the electrophysiological underpinnings of decision-making and reward processing in mTLE-UHS, contributing to the nuanced understanding of the condition's impact on cognitive function.

Study 2.

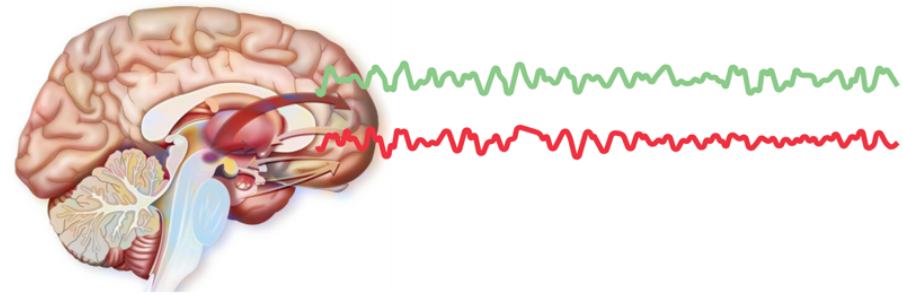
In our investigation, we employed a refined version of the functional Magnetic Resonance Imaging (fMRI) paradigm to probe the intricacies of reward processing mechanisms. The probabilistic gambling task paradigm was adapted to facilitate fMRI application, drawing from seminal frameworks established by preceding researchers. Participants engaged with a visual decision-making task, responding to numerical prompts designed to elicit cerebral responses indicative of reward valuation. The probabilistic gambling task sequence is initiated with a visual cue, followed by a decision-making interval and subsequent feedback phase, signaling monetary outcomes with color-coded indicators.

This tailored fMRI task was structured into three sequential runs, encompassing 180 trials that balanced the expected monetary value, thereby neutralizing decision-making biases. The design intricately wove standard and unexpected feedback types to foster a dynamic testing environment. Throughout the task, participants were periodically apprised of their cumulative virtual earnings, a motivational factor miming real-life incentive structures. This protocol facilitated mapping neural correlates underpinning reward processing, with precise spatial delineation during fMRI scanning.

Our fMRI assessment encompassing a longitudinal framework with two pivotal evaluation phases tailored to the nuances of our control and patient cohorts. The temporal spacing of these assessments was strategically determined to capture the evolution of neurocognitive profiles post-intervention, providing a comparative snapshot of the pre- and post-surgical cognitive milieu. Data acquisition leveraged the high-resolution

capabilities of a 3T MRI scanner, with subsequent preprocessing and analysis conducted within a robust statistical framework to ensure the precision and reliability of our findings. The data analysis was bifurcated into a probabilistic gambling task performance assessment and a univariate analysis of gain and loss trials at the whole-brain level. The latter incorporated a model of dynamic cerebral response and employed a general linear model to discern monetary gain and loss effects. This methodological rigor extended to the ROI analysis, where the statistical thresholding and anatomical labeling conformed to high standards of accuracy, allowing for a nuanced exploration of group differences and the valence-magnitude dynamics of neural activation.

The statistical analysis was replicated in a second evaluation phase, with additional ROI analyses that enabled a comprehensive understanding of group and session differences, employing sophisticated factorial models to elucidate differential cerebral activations and inform our understanding of the nuanced effects of epilepsy surgery on brain function.



CHAPTER II: ELECTROPHYSIOLOGICAL CORRELATES OF REWARD PROCESSING IN mTLE-UHS

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Reward-based decision-making in mesial temporal lobe epilepsy patients with unilateral hippocampal sclerosis pre- and post-surgery

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ABSTRACT

Background: Correct functioning of the reward processing system is critical for optimizing decision-making as well as preventing the development of addictions and/or neuropsychiatric symptoms such as depression, apathy, and anhedonia. Consequently, patients with mesial temporal lobe epilepsy due to unilateral hippocampal sclerosis (mTLE-UHS) represent an excellent opportunity to study the brain networks involved in this system.
Objective: The aim of the current study was to evaluate decision-making and the electrophysiological correlates of feedback processing in a sample of mTLE-UHS patients, compared to healthy controls. In addition, we assessed the impact of mesial temporal lobe surgical resection on these processes, as well as general, neuropsychological functioning.
Method: 17 mTLE-UHS patients and 17 matched healthy controls completed: [1] a computerized version of the Game of Dice Task, [2] a Standard Iowa Gambling Task, and [3] a modified ERP version of a probabilistic gambling task coupled with multichannel electroencephalography. Neuropsychological scores were also obtained both pre- and post-surgery.
Results: Behavioral analyses showed a pattern of increased risk for the mTLE-UHS group in decision-making under ambiguity compared to the control group. A decrease in the amplitude of the Feedback Related Negativity (FRN), a weaker effect of valence on delta power, and a general reduction of delta and theta power in the mTLE-UHS group, as compared to the control group, were also found. The beta-gamma activity associated with the delivery of positive reward was similar in both groups. Behavioral performance and electrophysiological measures did not worsen post-surgery.
Conclusions: Patients with mTLE-UHS showed impairments in decision-making under ambiguity, particularly when they had to make decisions based on the outcomes of their choices, but not in decision-making under risk. No group differences were observed in decision-making when feedbacks were random. These results might be explained by the abnormal feedback processing seen in the EEG activity of patients with mTLE-UHS, and by concomitant impairments in working memory, and memory. These impairments may be linked to the disruption

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of mesial temporal lobe networks. Finally, feedback processing and decision-making under ambiguity were already affected in mTLE-UHS patients pre-surgery and did not show evidence of clear worsening post-surgery.

1. Introduction

On a daily basis, the average person makes over 35,000 decisions, based on the costs and benefits associated to their actions. Both positive and negative outcomes serve to guide and reinforce future behavior according to internal monitoring processes, mediated primarily by individual sensitivity to reward (e.g., Padrão et al., 2013), but also by cognitive functions such as learning (Schultz, 2006; Marco-Pallares et al., 2008) and/or working memory (José et al., 2020).

Over the last couple of decades, feedback and reward-based decision-making have been associated with a sizeable brain network involving: the orbitofrontal cortex, ventromedial prefrontal cortex, ventral medial and dorsal lateral striatum/nucleus accumbens, anterior and posterior cingulate cortex, amygdala (McClure et al., 2004; Marco-Pallares et al., 2008; Wang, 2012; Hiser and Koenigs, 2018; Cox and Witten, 2019) and hippocampus (Johnson et al., 2007; Camara et al., 2009; Haber and Knutson, 2010; Ito and Lee, 2016; Vilà-Balló et al., 2017). In light of this, the study of patients with mesial temporal lobe epilepsy due to unilateral hippocampal sclerosis (mTLE-UHS) is crucial to determine how dysregulation of this network can affect the way in which, individuals process the positive and negative feedbacks associated with their actions, as well as motivational approach behaviors, and consequently, optimal decision-making.

Traditionally, decision-making has been studied in two situations (for review, see Liebherr et al., 2017). First, in decisions under risk, (e.g., Game of Dice Task, GDT), where the rules are explicit and the winning probabilities are known. In these tasks, the probabilities (not necessarily directly given) of gaining or losing can be calculated from the beginning. Second, in decisions under ambiguity, where no explicit information about the consequences of each decision is given, such as in behavioral gambling tasks (e.g., IOWA Gambling Task, IGT), where participants need to learn the consequences of their choices from feedback processing. Nevertheless, throughout the task, participants can learn the magnitude and the probability of the gains and losses associated with each choice, which should lead to the selection of advantageous options. Importantly, while the rules are being acquired, decision-making in tasks under ambiguity is equivalent to that of decision-making in tasks under risk. Moreover, alternative versions of the gambling tasks (Gehring and Willoughby, 2002; Marco-Pallares et al., 2008) have been developed without any underlying structure or rules, whereby rewards and punishments are delivered at random. In these tasks, behavior is guided by internal expectations rather than objective probabilities, which is more suitable for isolating electrophysiological markers of feedback processing, at a cost of evaluating behavioral and learning effects (Severo et al., 2020).

For the purpose of unraveling individual differences associated with feedback processing, gambling tasks have been combined with simultaneous electroencephalographic (EEG) recordings to obtain Event-Related Potentials (ERPs) and Event-Related Oscillations (EROs) (Chandrakumar et al., 2018). In particular, a frontocentral negative ERP component appears and peaks around 250–300 ms post-feedback onset, which has been related to frontal theta oscillatory activity (4–7 Hz, 200–450 ms). Both ERP negativity and theta activity are larger after monetary losses than gains (Gehring and Willoughby, 2002; Marco-Pallares et al., 2008; Vega et al., 2013). However, the negativity of this component overlaps with a frontocentral positivity, associated with delta activity (1–4 Hz, 200–400 ms), with a centroparietal distribution, which appears in response to monetary gains. The difference between gain- and loss-associated activity has been termed the Feedback-Related Negativity (FRN, also known as Reward Positivity, RewP, or Medial Frontal Negativity, MFN) (Bernat et al., 2011, 2015; Foti et al., 2015; Williams et al., 2021). Finally, frontal beta-gamma oscillatory activity (20–35 Hz), considered a measure of consummatory reactions to positive outcomes (monetary gains) (Marco-Pallares et al., 2008; Hajihosseini et al., 2012), is associated with later latencies than the FRN.

Concerning patients with mTLE-UHS (for a review, see Zhang et al., 2018), no impairments have been reported in decision-making under risk when patients can estimate risks using rational strategies, such as in GDTs (Labudda et al., 2009) or Probabilistic-Associated Gambling Tasks (Delazer et al., 2010). Nevertheless, it has been observed that patients with mTLE-UHS fail at decision-making under ambiguity (e.g., on the IGT), by selecting less advantageous choices, especially towards the end of the task, therefore evidencing problems in learning the rules or task contingencies (Labudda et al., 2009; Delazer et al., 2010; Yamano et al., 2011; Xie et al., 2013). Similarly, in a probabilistic, reversal learning task, patients with mTLE-UHS were unable to correctly reverse their disadvantageous choices to more advantageous ones, despite receiving probabilistic feedback after each choice (Vilà-Balló et al., 2017). Similar results have been previously reported in post-surgical patients with mTLE-UHSs (surgically treated with an anterior temporal lobectomy that included amygdalohippocampectomy) (Bonatti et al., 2009; Von Siebenthal et al., 2017). However, the impairments in feedback processing associated with these deficits remain unclear.

The main goal of the current study was to evaluate decision-making and the electrophysiological correlates of feedback processing in patients with mTLE-UHS before and after anterior mesial temporal lobe resection surgery. To this aim, we used an integrative longitudinal design combining behavioral data, ERPs, EROs, neuropsychological assessments, and a healthy, control group. To the best of our knowledge, no previous studies have addressed this issue with a similar design. Our study consisted of: (i) replicating previous behavioral studies on patients with mTLE-UHS, employing the IGT and the GDT, two tasks showing high behavioral sensitivity; and (ii) evaluating ERPs and EROs during a probabilistic gambling task with no underlying structure (Marco-Pallares et al., 2008). Despite minor behavioral sensitivity, this paradigm was selected because it is optimal for obtaining very reliable feedback-related ERP components (e.g. the FRN component) as well as oscillatory modulations (delta, theta, and beta-gamma oscillatory activities) (Gehring and Willoughby, 2002; Marco-Pallares et al., 2008; Marco-Pallarés et al., 2009; Foti et al., 2015; Vilà-Balló et al., 2015; Watts et al., 2017); (iii) obtaining neuropsychological scores in different cognitive domains to obtain a cognitive profile of our sample; finally (iv) performing an initial assessment and follow-up, to understand the impact of surgery on all of the evaluated processes in patients with mTLE-UHS.

Based on previous findings, we hypothesized that compared to controls, patients with mTLE-UHS will show: (i) an increased preference for disadvantageous decks during the IGT (especially during the final blocks) but not on the GDT (Labudda et al., 2009; Delazer et al., 2010; Yamano et al., 2011; Xie et al., 2013; Zhang et al., 2018) (ii) an abnormal feedback-related electrophysiological activity on the gambling task (Johnson et al., 2007; Camara et al., 2009; Haber and Knutson, 2010; Ito and Lee, 2016; Vilà-Balló et al., 2017); (iii) lower neuropsychological scores in memory and verbal domains (Lee et al., 2002; Roger et al., 2020); and (iv) despite not being previously addressed, we expect a general worsening of patient deficits post-surgery (Zhang et al., 2018).

2. Method

2.1. Participants

The mTLE-UHS group consisted of seventeen patients with either left

(ten patients; seven females) or right (seven patients; three females) hemisphere damage. All patients had refractory mTLE and were recruited after a presurgical evaluation at the Bellvitge University Hospital as candidates for anterior mesial temporal resection surgery. Patient diagnosis was established using clinical EEG and magnetic resonance imaging. All patients underwent a neurological and neuropsychological examination, as well as continuous video-EEG monitoring. Patients were evaluated before and at least three months after an anterior mesial temporal lobe resection for the relief of medically intractable mTLE. The surgery, performed by the same neurosurgeon each time, consisted of *en bloc* resection of the mesial temporal structures. Hippocampal sclerosis was confirmed in all patients with a histopathological study by the same pathologists. None of the patients suffered a seizure 24 h prior or during the experimental task, and all of them were on regular antiseizure medication. In the current study, the mTLE-UHS group was matched for age (Patients: 40.8 ± 12.8; Controls: 40.7 ± 15.5; t (32) = 0.012, p = 0.990), sex (Patients: 10F, 7 M; Controls: 9F,8M; X^2 (1, N = 34) = 0.119, p =.730) and years of education (Patients: 11.7 ± 4.2; Controls: 11.1 ± 4.5; t (32) = 0.394, p = 0.696) with a healthy control group. The Ethical Committee of the Bellvitge University Hospital approved the study (PR064/10). Informed consent was obtained from all of the participants. Descriptive data are reported in Table 1.

2.2. Neuropsychological assessment

All of the participants (patients and controls) completed the: Logical memory I (immediate verbal memory) and II (delayed verbal memory), Visual reproduction I (immediate visual memory) and II (delayed visual memory), Digit Span and Letter Number subtests of the Wechsler Memory Scale III (Wechsler, 2004); Vocabulary subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1999); Rey Auditory Verbal Learning Test (Rey, 1941; Schmidt, 1996), Trail Making Test (TMT-A and TMT-B) (Reitan, 1955; Davies, 1968), Boston Naming Test (BNT) (Kaplan et al., 2001), Semantic Fluency and Phonemic Fluency subtest of the Barcelona Test-R (Peña-Casanova, 2005), and the Rey-Osterrieth Complex Figure (copy, time, and memory) (RCF, Rey, 1941; Osterrieth, 1944; Peña-Casanova, 2005). To compare the neuropsychological functioning in patients with mTLE-UHS before and after surgical resection, results from the above-mentioned tests were grouped into seven standard cognitive domains (Riley et al., 2010; Chang et al., 2012; Palta et al., 2014; Kellermann et al., 2016; Allone et al., 2017): verbal comprehension, processing speed, verbal functioning, verbal memory, constructional ability, visuospatial memory, and working memory. Neuropsychological data for all participants are summarized in Table 2.

2.3. Behavioral game of dice task

We used a simplified, modified version of the computerized GDT (Brand et al., 2005). On each round (trial), participants saw one dice, a panel indicating the balance after each choice, the accumulated capital, and the result of the current throw (Fig. 1A). In contrast to the original version of the task (Brand et al., 2005), no dice shaker was shown and the dice was blank (no numbers) at the beginning of the round, prior to the throw. Participants began the task with a starting virtual capital of 1000€ and were instructed to attempt to increase this capital by throwing one dice during 18 rounds. Before the throw, participants had to guess which number would appear on the dice. They could guess one

Table 1
Demographic data for the patients with mTLE-UHS (left and right) and controls included in this study. Age, sex, years of education (Educ.). Pre-surgery clinical information (at the initial evaluation) for patients with mTLE-UHS, including age at epilepsy onset (Onset), disease duration in years (Dis. Duration), seizure frequency (days/month), presence of focal impaired awareness seizures (FIAS), presence of focal to bilateral tonic-clonic Seizures (FBTCS), number of antiseizure drugs (Num. ASD), and benzodiazepine (BZD), barbiturates (BARB), and Phenobarbital (PB).

Code	Group	Age	Sex	Educ.	Onset	Dis. Duration	Freq	FIAS	FBTCS	Num. AEDS	BZD, BARB, & PB
ep_02	TLE-L	39	F	8	14 M	37Y	1–2/mo	Yes	Yes	3	clobazam 10 mg/d
ep_05	TLE-R	36	M	11	18Y	19Y	4–6/mo	Yes	Yes	3	PB 100 mg/d
ep_08	TLE-R	50	F	8	18Y	33Y	6–8/mo	Yes	Yes	3	PB 100 mg/d
ep_09	TLE-L	65	F	0	4Y	59Y	4–5/mo	Yes	Yes	2	PB 100 mg/d
ep_10	TLE-R	66	M	8	41Y	25Y	4/mo	Yes	No	2	No
ep_11	TLE-L	33	F	11	16Y	17Y	30–35/mo	Yes	Yes	3	Clobazam 10 mg/d
ep_12	TLE-L	34	M	16	23Y	9Y	8–10/mo	Yes	Yes	2	No
ep_13	TLE-L	38	M	16	32Y	8Y	2–4/mo	Yes	Yes	3	No
ep_14	TLE-R	21	M	16	17Y	6Y	5/mo	Yes	Yes	2	No
ep_15	TLE-L	37	F	12	13 M	48Y	7–9/mo	Yes	No	2	No
ep_18	TLE-L	41	F	14	12 M	32Y	5–6/mo	Yes	Yes	4	PB 150 mg/d
ep_21	TLE-D	61	F	12	31Y	31Y	4–5/mo	Yes	Yes	3	No
ep_22	TLE-L	29	M	14	15Y	16Y	3–4/mo	Yes	Yes	3	PB 200 mg/d
ep_25	TLE-L	25	M	9	13Y	13Y	1/mo	Yes	Yes	2	No
ep_29	TLE-R	34	F	12	21Y	13Y	2/mo	Yes	Yes	2	No
ep_34	TLE-L	43	F	14	8Y	38Y	18–20/mo	Yes	Yes	2	No
ep_35	TLE-L	35	F	17	2Y	33Y	4–6/mo	Yes	Yes	2	No
c_02	Control	42	F	10							
c_05	Control	39	M	10							
c_06	Control	28	F	11							
c_07	Control	35	F	16							
c_08	Control	53	F	8							
c_09	Control	68	F	6							
c_10	Control	71	M	0							
c_11	Control	25	F	17							
c_12	Control	30	M	14							
c_14	Control	25	M	17							
c_15	Control	43	F	10							
c_18	Control	43	F	10							
c_19	Control	29	F	18							
c_21	Control	61	M	10							
c_22	Control	28	M	12							
c_25	Control	21	M	13							
c_27	Control	51	F	12							

Table 2
Demographic information for the controls and patients with mTLE-UHS included in this study. Age, years of education (Educ.). Mean scores of neuropsychological data for first and second evaluations, for controls and patients with mTLE-UHS. The neuropsychological measures are: LMI (Logical Memory I), LMII (Logical Memory II), VRI (Visual Reproduction I), VRII (Visual Reproduction II), Dig. span (Digit Span), Letter num. (Letters and numbers), RAVLT A1 and A5 (total learning at trials 1 and 5), RAVLT A6 (immediate recall), RAVLT A7 (delayed recall), RAVLT Rcog (recognition), TMT A (Trial Making Test A), TMT B (Trial Making Test B), Voc. (Vocabulary), BNT (Boston Naming Test), Flue. (s) (Semantic Fluency), and Flue. (p) (Phonemic Fluency), RCF Copy (Rey-Osterrieth Complex Figure, RCF, copy), RCF Time (RCF copy time), and RCF recall (RCF immediate recall). Group comparisons were performed using two sample *t*-tests or rmANOVAs. Results were grouped into six domains: Verbal comprehension, verbal functioning, verbal memory, constructional ability, visuospatial memory, and attention, working memory, and executive function.

		CONTROLS M (SD)		**mTLE-UHS M (SD)**		**t**	**Sig.**				
	Age	40.71 (15.48)		40.76 (12.84)			−0.120	0.990			
	Educ	11.06 (4.48)		11.65 (4.23)			−0.394	0.696			
		First evaluation	**Second Evaluation**	**First evaluation**	**Second evaluation**	**Evaluation**		**Evaluation × Group**		**Group**	
		M (SD)	**M (SD)**	**M (SD)**	**M (SD)**	**F**	**Sig.**	**F**	**Sig.**	**F**	**Sig.**
Verbal comprehension	Voc	41.76 (11.97)	44.41 (10.99)	33.77 (8.17)	35.31 (9.39)	3.282	0.081	0.230	0.635	5.449	**0.027**
Processing speed	TMT A	50.53 (32.85)	45.06 (42.29)	49.76 (25.58)	48.53 (28.43)	1.005	0.324	0.401	0.531	0.016	0.901
	TMT B	96.88 (76.92)	74.25 (31.69)	152.56 (141.95)	130.63 (85.50)	2.651	0.114	0.001	0.980	3.539	0.070
Verbal functioning	BNT	50.65 (9.02)	52.41 (8.44)	48.59 (6.59)	43.76 (9.40)	3.638	0.065	16.877	**0.000**	3.712	0.063
	Flue. (s)	19.29 (5.80)	20.82 (7.18)	17.82 (5.93)	15.94 (4.72)	0.040	0.843	3.734	0.062	2.955	0.095
	Flue. (p)	14.35 (5.44)	14.88 (5.43)	12.88 (6.34)	12.76 (5.73)	0.054	0.818	0.134	0.717	1.037	0.316
Verbal memory	LMI	32.76 (13.93)	40.35 (14.03)	29.12 (9.59)	25.82 (11.33)	1.719	0.199	11.040	**0.002**	5.402	**0.027**
	LMII	21.53 (10.04)	26.65 (10.43)	15.88 (7.91)	13.29 (7.55)	1.366	0.251	12.679	**0.001**	10.603	**0.003**
	RAVLT A1	5.82 (2.30)	5.65 (2.67)	5.53 (1.70)	4.53 (1.66)	2.317	0.138	1.135	0.295	1.306	0.262
	RAVLT A5	13.12 (1.83)	12.94 (2.22)	11.53 (2.79)	9.82 (3.07)	7.087	**0.012**	4.678	**0.038**	8.873	**0.005**
	RAVLT A6	11.65 (3.55)	11.65 (3.22)	8.82 (3.49)	6.47 (4.08)	3.553	0.069	3.553	0.069	14.118	**0.001**
	RAVLT A7	11.59 (3.78)	11.35 (3.52)	8.71 (3.67)	7.29 (4.21)	2.418	0.130	1.234	0.275	8.482	**0.006**
	RAVLT Recog	13.76 (2.36)	14.06 (1.60)	12.76 (2.51)	12.71 (1.45)	0.079	0.780	0.178	0.676	4.446	**0.043**
Constructional ability	RCF Copy	36.00 (14.56)	32.26 (7.63)	30.96 (7.81)	32.14 (5.02)	0.239	0.628	0.884	0.355	1.232	0.276
	RCF Time	169.41 (72.47)	172.00 (90.18)	175.15 (71.11)	192.85 (101.92)	1.027	0.320	0.570	0.457	0.204	0.655
Visuospatial memory	VRI	86.47 (22.66)	88.06 (23.90)	74.59 (20.36)	72.88 (21.58)	0.001	0.976	0.746	0.394	3.380	0.075
	VRII	76.00 (27.72)	82.88 (25.72)	55.18 (26.99)	54.76 (25.02)	1.350	0.254	1.715	0.200	8.079	**0.008**
	RCF Recall	21.03 (8.57)	23.34 (9.96)	15.53 (8.12)	12.46 (5.50)	0.237	0.630	6.617	**0.016**	8.327	**0.007**
Working memory	Dig. span	15.18 (4.90)	16.00 (5.56)	11.71 (3.65)	11.65 (3.33)	0.897	0.351	1.194	0.283	7.047	**0.012**
	Letter num.	9.24 (3.70)	10.24 (3.67)	8.06 (2.38)	7.06 (3.53)	0.000	1.000	7.406	**0.011**	3.787	0.061

Note: The N for all of the analyses was 17 per group, with the following exceptions in which there was missing data. Control, second evaluation (TMT-B N = 16, RCF recall N = 16); mTLE-UHS, first evaluation (TMT-B N = 16, RCF copy N = 16, RCF time N = 16, RCF recall N = 16, letters and numbers N = 16); mTLE-UHS, second evaluation (Voc N = 13, TMT-B N = 16, RCF copy N = 14, RCF time N = 13, RCF recall N = 14). For all of the reported analyses, only participants with complete data in both evaluations were included. Significant results are highlighted in bold. P-values were not corrected for multiple comparisons.

number (e.g., one) or a combination of two (e.g., one and two), three, or four numbers. Importantly, during each round, there was only one throw of one dice, consequently, the more numbers were selected, the greater the probability to guess the number that would appear on the dice.

In our version of the task, participants were free to choose one, two, three, or four numbers, but they could not select the specific numbers included in each choice as these were fixed and adjusted between rounds (for an example, see the combination of numbers in Fig. 1A). Each choice was associated with a virtual amount of money and the participants bet: 1000€ on one single number, 500€ on two numbers, 200€ on three numbers, and 100€ on four numbers. Selection of the choice was carried out by pressing the Z, X, N, or M buttons of the keyboard, with the middle or index finger of the left or right hand, depending on the choice. Then, after the virtual throw, and during 5000 ms, a number was presented on the dice and participants were informed in the balance panel if they won or lost the previously chosen amount of money. Then, after 1000 ms, the next round began and new numbers were presented. The rules, as well as the extent of gains and losses, were explicitly described and visualized during this task. The probability of winning could be deduced through the occurrence ratio (1:6, 2:6, 3:6, 4:6). Therefore, choosing either one or two numbers make up the disadvantageous conditions, whereas selecting three or four numbers constitutes the advantageous ones. For example, if a participant decided to guess one, two, three or four numbers each time, then the final balance (taking into account the starting capital and the accumulated outcomes) after 18 rounds would be −11.000€, −2000€, 1000€, or 1600€, respectively. The results of the throws were pseudo-randomized across the task, with each number appearing three times but in a balanced order. See Fig. 1A for a schematic illustration of the GDT.

2.4. Standard behavioral IOWA gambling task

We used a computerized version of the IGT (see Fig. 1B) designed by Bechara et al. (1994). Four rectangles were presented in the middle of the screen, representing decks of cards, labeled A, B, C, and D on the bottom end. On each trial, participants had to select one card from any of the four decks, by pressing the Z (deck A), X (deck B), N (deck C), or M (deck D) buttons of the keyboard, with the middle or index finger of the left or right hand. After the selection was made, a red or black "0″, representing a red or black card respectively, was displayed in the middle of the selected card. After each card had been selected, the participants received some amount of virtual money, which varied depending on the deck, and was displayed on the top of the screen (e.g., "You win 100€"). Specifically, participants received 100€ for each card selected from decks A and B and 50€ for each card selected from decks C and D. However, there were some penalty cards in each deck. The penalty was announced once the card selection had been made, and was displayed on the same deck with a "negative red number" (replacing the red 0), but also below the message indicating the win (e.g., "You lost 250€"). Importantly, when the selected card did not contain a penalty, a

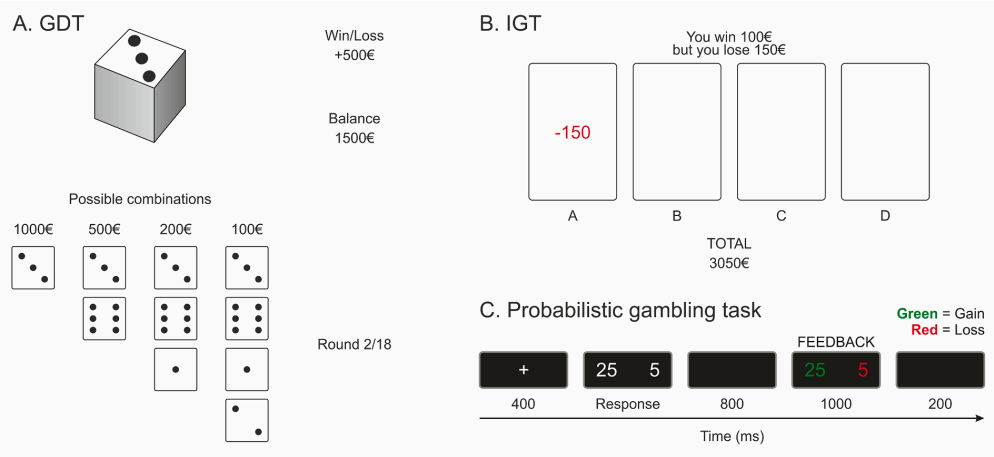

Fig. 1. A. A schematic illustration of the GDT. In this example, the participant was in the second round out of a total of 18 rounds, and pressed the X button of the keyboard with the index finger of the left hand. Consequently, the participant selected the option of two numbers (bet = 500€), which included the numbers three and six. After the throw, the number on the dice was three, and consequently the participant won 500€. The balance was updated and this amount was added to the initial capital of 1000€. **B.** An illustration of the IOWA. In this example, the participant selected deck A by pressing the Z button of the keyboard with the middle finger of their left hand. The selection of this deck involved winning 100€. However, the participant obtained a penalty of 150€. The total balance was updated taking into account both outcomes. **C.** The sequence of stimulus and response events in the probabilistic gambling task used in the present study (Marco-Pallarés et al., 2009). After a warning signal, a pair of numbers ([5 2 5] or [2 5 5]) was presented, and participants were instructed to select one of the two alternatives by pressing the corresponding button on the left- or right-hand side (response choice). One second after the response choice, one of the numbers turned red and the other green (feedback), indicating a gain (green) or loss (red) of the corresponding amount of virtual money in Euro cents.

red or black zero appeared in the middle of the screen. The penalties varied based on the decks, and their positions in the decks were fixed (same position for all participants). The duration of the task was fixed to 100 card selections. Each deck of cards was programmed to contain 40 cards, 20 with a black face and 20 with a red face. The back of the cards was represented with a white vertical rectangle inside a black frame (see Fig. 1B). For each deck, the fixed order of black and red cards, as well as penalties, was programmed according to the original version of Bechara et al. (1994), keeping in mind that we replaced American Dollar values with Euros. Specifically for deck A, on every 10 cards, participants won 1000€ but there were five unpredictable punishments from 150€ to 350€, leading to a total loss of 1250€. On the other hand, for every 10 cards from deck B the gain was 1000€, and there was only one penalty of 1250€ in the deck. Decks A and B were equivalent in that both of them produced a total net loss of 250€ every 10 trials, and were disadvantageous over the long term. For deck C, however, every 10 cards led to a gain of 500€, with five unpredictable penalties from 25€ to 75€, generating a total loss of 250€. Similarly, the gain after selecting 10 cards from deck D was 500€, but there was a single penalty of 250€. Decks C and D were equivalent in producing an overall net gain of 250€, and were advantageous over the long term. If a participant selected 40 cards from the same deck, the deck was finished (indicated by a black, dashed line displayed in the middle of the deck), and the participant had to choose cards from the other decks for the remainder of the game. Participants began with a virtual credit amount of 2000€ and were informed that some decks were better than others. They were also instructed to avoid the disadvantageous decks and choose the advantageous ones, to win as much virtual money as possible. On each trial, participants could select one card from any deck and they were also permitted to switch between decks from trial to trial. Participants were able to see their accumulated capital throughout the entire task.

2.5. Probabilistic gambling task

A modified ERP version of the probabilistic gambling task (Marco-Pallares et al., 2008) was employed, similar to the one described by Gehring and Willoughby (2002). In this task, two numbers (25 and 5) were presented in the middle of a computer screen (Marco-Pallarés et al., 2009; Camara et al., 2010). Only two possible displays were given, either [2 5 5] or [5 2 5] (see Fig. 1C).

Participants were required to choose the number they wanted to bet on, and press either the left or right mouse button with their right index finger, depending on their choice. For example, in a [2 5 5] display, pressing the left button indicated the selection of the number 25, and pressing the right button indicated the selection of the number 5. After this step (with a fixed interval of 800 ms), one of the numbers turned red while the other turned green. If the selected number changed to red, the participant lost the corresponding amount in virtual Euro cents, whereas if the subject's chosen number turned green, they won this amount in virtual Euro cents. The duration of the feedback stimulus was 800 ms. The subsequent trial began after 200 ms with the presentation of a warning signal ("+", lasting 400 ms), followed by a new pair of numbers.

The experiment consisted of 17 blocks of 40 trials. In each block, four different feedback types were presented in random order: [**2 5** 5], [2 **5** **5**], [**5** 2 5], and [**5 2 5**] (note: nonbold font stands for red [a loss], while bold font indicates green [a win]). Participants were encouraged to gain as much as possible. Combined with the two response options, this yielded eight different types of stimuli–response combinations. For example, if the participant chose the left number in a [2 5 5] event, this was scored as a "maximum gain" trial. However, if the participant opted for the right number, the trial was scored as a minimum loss.

Importantly, the mean expected value of the monetary outcome was zero on each block, to avoid potential confounding influences of a differential probability of gains or losses. The participants were informed about their accumulated amount of money (10 s duration) after each mini-block of ten trials.

3. EEG acquisition

EEG was recorded continuously (digitized, with a sampling rate of

250 Hz, bandpass from 0.01 to 70 Hz) using a BrainAmp amplifier, from 29 tin electrodes that were mounted on an elastic cap and located at standard positions (FP1/2, F3/4, C3/4, *P*3/4, O1/2, F7/8, T3/4, T5/6, Fz, Cz, Pz, FC1/2, FC5/6, CP1/2, CP5/6, PO1/2). The EEG was referenced on-line to the right ocular canthus. Biosignals were re-referenced offline to the two mastoid electrodes' mean activity. Electrode impedances were maintained below 5kΩ. Vertical eye movements were monitored by an electrode placed below the right eye.

3.1. Procedure

This study followed a longitudinal design and was comprised of three initial sessions and three follow-up sessions performed after surgery and always at least six months after the first initial sessions for all participants to reduce learning effects.

A trained clinician performed the neuropsychological assessment for each participant during the first session. A second session was conducted between one to seven days after the first session and included the GDT and the IGT. Then, participants completed the EEG session between one to seven days later. The procedure was identical in the follow-up sessions.

Throughout the manuscript, we will refer to these initial sessions as "the first evaluation", and the follow-up sessions as "the second evaluation". It is important to note that between both evaluations, the patients with mTLE-UHS underwent surgery, which was performed at least three months prior to the second evaluation (Bonelli et al., 2010, 2013).

3.2. Data processing

Feedback-locked ERPs were separately averaged for gain (combining maximum gain [+25] and minimum gain [+5]) and loss trials (combining maximum loss [−25] and minimum loss [−5]), from 100 ms before the feedback (baseline) to 924 ms after it. Epochs that exceeded ± 100 μV, on the electrooculogram (EOG) or EEG, were removed offline for further analysis using the extreme value function of the EEGLAB toolbox. For behavioral and electrophysiological analyses, only reaction times (RT) occurring between 120 and 750 ms post-stimulus presentation were considered for the analyses (Krämer et al., 2007). All artifact-free error trials were included regardless of subsequent correct responses.

To study the EROs elicited by the feedbacks, 4000 ms epochs were generated (epochs that comprised ± 2000 ms before and after the feedbacks). Epochs that exceeded ± 100 μV in the EOG or EEG were removed offline from further analyses using the EEGLAB toolbox. A 100 ms time range before the feedback was defined as the baseline. Single-trial data was convoluted using a 6-cycles complex Morlet wavelet (Tallon-Baudry et al., 1997). Changes in time-varying energy (square of the convolution between wavelet and signal), in the studied frequencies (from 1 to 40 Hz; linear increase), concerning baseline, were computed for each trial and averaged for each subject before performing a grand average.

The EEG artefact rejection rate was similar between groups and evaluations (first evaluation: controls 16.7 ± 21.0 %, TLE-UHS 28.7 ± 24.8 %; second evaluation: controls 17.9 ± 22.3 %, TLE-UHS 26.2 ± 24.9); main effect of group: $F(1,32) = 1.857$, $p = 0.182$; main effect of evaluation: $F(1,32) = 0.031$, $p = 0.861$).

3.3. Statistical analysis

For each neuropsychological measure, we performed a repeated-measures analysis of variance (rmANOVA), including Evaluation (Level 1: First, Level 2: Second) as within-subjects factor and Group (Level 1: mTLE-UHS, Level 2: Controls) as between-subjects factor.

Statistical analysis of the GDT was performed on the proportion of disadvantageous choices and using a rmANOVA. We included Evaluation (Level 1: First, Level 2: Second) as within-subjects factor, and Group (Level 1: mTLE-UHS, Level 2: Controls) as between-subjects factor.

Similarly, for the IGT we used a rmANOVA with Block (Level 1 to 5, including blocks 1 to 5, respectively) and Evaluation (Level 1: First, Level 2: Second) as within-subjects factors, and Group (Level 1: mTLE-UHS, Level 2: Controls) as a between-subjects factor, on the frequency of advantageous choices (C + D) minus the frequency of disadvantageous choices (A + B).

For the probabilistic gambling task, we assessed the tendency to bet 25 (risky choice) during the task. On this data, we performed a rmANOVA with Evaluation (Level 1: First, Level 2: Second) as within-subjects factors, and Group (Level 1: mTLE-UHS, Level 2: Controls) as between-subjects factor.

All of the electrophysiological analyses, electrode selection, time-windows, and frequency ranges (for the time–frequency analyses), were based on current data (peak amplitude or maximum power value of each range), but also on previous literature.

For the feedback-locked ERP analysis, separately for gains and losses, and for the first and second evaluations, we computed the mean amplitude at 260–310 ms time-window after feedback presentation, centered on the peak of the component at FC2 electrode, based on previous literature using the same Gambling Task (Marco-Pallares et al., 2008; Padrão et al., 2013; Vega et al., 2013). Then, we carried out a rmANOVA on the mean amplitude, with Valence (Level 1: Gain, Level 2: Loss) and Evaluation (Level 1: First, Level 2: Second) as within-subjects factors, and Group (Level 1: mTLE-UHS, Level 2: Controls) as a between-subjects factor. Please, note that the amplitude difference between both levels of Valence constitutes the FRN.

A similar procedure was used for feedback-locked ERO analyses to obtain delta, theta, and beta-gamma frequency ranges, for which we computed the mean power for each specific range, separately for gains and losses, and for the first and second evaluations. For the delta activity, we selected a region of interest (ROI) of electrodes (*P*3, PZ *P*4, PO1, PO2). This selection was done by considering the maximum power value and the widespread parietal distribution of the delta activity obtained in the current study, but also on previous literature indicating that this activity could have a widespread distribution from centroparietal electrodes (Cavanagh, 2015; Pornpattananangkul and Nusslock, 2016). Taking into account these studies and the current distribution, the term parietal delta activity will be used throughout the manuscript. We obtained the mean power at 3–4 Hz between 250 and 350 ms based on the activity peak (Williams et al., 2021). Then, we performed a rmANOVA on the mean power, with Valence (Level 1: Gain, Level 2: Loss) and Evaluation (Level 1: First, Level 2: Second) as within-subjects factors, and Group (Level 1: mTLE-UHS, Level 2: Controls) as a between-subjects factor. For both theta and beta-gamma activities, there is clear evidence of their main frontal distribution. However, since the frontal theta activity has a focal distribution and the frontal beta-gamma activity has a widespread distribution, we decided to use a single electrode for the former and a ROI analysis for the later (Marco-Pallares et al., 2008; Padrão et al., 2013; Vega et al., 2013; Williams et al., 2021). With regard to the frontal theta activity, we calculated the mean power between 4 and 5 Hz and 300–400 ms (Williams et al., 2021) at FC2 electrode (Marco-Pallares et al., 2008; Padrão et al., 2013; Vega et al., 2013), and we performed a rmANOVA on the mean power with the same factors. For the frontal beta-gamma band range, we performed an analysis between 27 and 32 Hz and 330–430 ms. As previously mentioned, following previous studies indicating its frontal distribution, we selected a ROI (F3, FZ, F4, FC1, FC2) of electrodes (Marco-Pallares et al., 2008; Padrão et al., 2013; Vega et al., 2013). Then we performed a rmANOVA on the mean power with the same factors as the ones explained above. For the decomposition of the significant interactions, we used pairwise two-tailed *t*-tests for independent sample comparisons, or two-tailed paired t-tests to delineate specific effects in each group. For all statistical effects involving two or more degrees of freedom in the numerator, the Greenhouse-Geisser epsilon was used to correct possible violations of the sphericity assumption (Jennings and Wood, 1976). P-

values after correction are reported.

Finally, as an additional exploratory analysis, Pearson correlations were carried out to evaluate the relationship between clinical variables in mTLE-UHS (i.e., age at epilepsy onset, disease duration, and seizure frequency (days/month)) and the electrophysiological measures (i.e., amplitude of the FRN (loss minus gain), delta power difference (gain minus loss)), mean delta power (mean between gain and loss), and mean theta power (mean between gain and loss), at the first evaluation.

4. Results

4.1. Neuropsychological results

Mean neuropsychological test scores in patients with mTLE-UHS and healthy controls for the first and second evaluations, along with statistical analyses are reported in Table 2.

A significant main effect of group in the rmANOVAs revealed that patients with mTLE-UHS performed worse than controls on tests related to: verbal comprehension (Vocabulary), verbal memory (LMI, LMII, RAVLT A5, RAVLT A6, RAVLT A7, RAVLT Recog), visuospatial memory (VRII, RCF Recall) and working memory (Digit span) domains. A statistically significant Group × Evaluation interaction and posterior t-tests indicated that: (i) the patients with mTLE-UHS showed a worsening in verbal functioning (BNT) and verbal memory (RAVLT A5) on the second evaluation (see Table 2); and (ii) healthy controls showed a learning effect (better performance on the second, as compared to the first evaluation) on verbal functioning (BNT), verbal memory (LMI, LMII, RAVLT A5), visuospatial memory (RCF recall) and working memory (Letter num). It is important to note that patients with mTLE-UHS did not exhibit the same learning effect as controls, across sessions.

4.2. Behavioral performance in decision-making

Decision-making performance was assessed using the behavioral GDT and IGT tasks (see Fig. 2), as well as the ERP monetary gambling task.

GDT. For this analysis, we obtained the proportion of disadvantageous choices as compared to the total number of choices (see Fig. 2A). The rmANOVA revealed no difference between evaluations [main effect of Evaluation: $F(1,29) = 1.02$, $p = .319$]. Consistent with previous literature (Labudda et al., 2009), no differences were encountered between patients with mTLE-UHS [First evaluation: $M = 0.29$, $SD = 0.19$; Second evaluation: $M = 0.27$, $SD = 0.21$] and controls [First evaluation: $M = 0.28$, $SD = 0.20$; Second evaluation: $M = 0.35$, $SD = 0.22$], as indicated by the absence of a significant main effect of Group [$F(1,29) = 0.21$, $p = .65$] and Group × Evaluation interaction [$F(1,29) = 1.56$, $p = .222$] (Fig. 2A).

IGT. The rmANOVA on the frequency of advantageous choices (C + D) minus the frequency of disadvantageous choices (A + B), in the IGT (see Fig. 2B), revealed a significant main effect of Block [$F(4,120) = 8.5$, $p < .001$], in that participants selected more disadvantageous choices in the first blocks, and more advantageous choices in the final blocks. The main effect of Evaluation [$F(1,30) = 0.04$, $p = .847$] together with the Block × Evaluation interaction [$F(4,120) = 0.74$, $p = .562$] were not significant and showed no differences in performance across evaluations. Importantly, the mTLE-UHS group selected more disadvantageous choices than the control group [main effect of Group: $F(1,30) = 4.25$, $p = .048$] (see Fig. 2B). No significant interactions involving Group were observed [Block × Group: $F(4,30) = 1.04$, $p = .381$; Evaluation × Group: $F(4,30) = 0.03$, $p = .867$; Block × Evaluation × Group: $F(4,120) = 0.72$, $p = .562$].

Probabilistic gambling task. For the analysis of the probabilistic gambling task, we computed the probability of choosing 25 (risky choice) during the task. The rmANOVA revealed no differences between evaluations [main effect of Evaluation: $F(1,32) = 0.20$, $p = .66$]. We did not observe any significant difference between controls (First evaluation: 0.54 ± 0.09; Second evaluation: 0.56 ± 0.07) and patients with mTLE-UHS (First evaluation: 0.56 ± 0.10; Second evaluation: 0.52 ± 0.12), in the main effect of Group [$F(1,32) = 0.32$, $p = .575$] or the Evaluation × Group interaction [$F(1,32) = 2.25$, $p = .144$].

4.3. ERP analysis

Fig. 3 shows feedback-locked ERPs for loss and gain trials and for both groups and evaluations. A typical FRN component, described as the amplitude difference between loss and gain trials, and peaking at about 285 ms (Gehring and Willoughby, 2002; Marco-Pallares et al., 2008), was observed for both groups. Visual inspection would suggest that it was reduced for patients with mTLE-UHS as compared to controls. We selected the activity at FC2 electrode, the location with the largest FRN peak amplitude (Gehring and Willoughby, 2002; Marco-Pallares et al., 2008) and performed a rmANOVA at FC2 electrode, with two within-subjects factors, Valence (Gain, Loss) and Evaluation (First, Second) (included Group as between-subjects factor). Please note that, the Valence factor captured the amplitude difference (difference waveform) between loss and gain trials and represents the FRN component. The significant main effect of Valence [$F(1,32) = 13.89$, $p = .001$] corroborated the increased frontal negativity for losses as compared to gains, and consequently, the presence of the FRN. Interestingly, the significant main effect of Evaluation [$F(1,32) = 4.48$, $p = .042$] indicated that overall, there was more negativity at the second compared to the first evaluation [no significant interaction was observed for Valence and

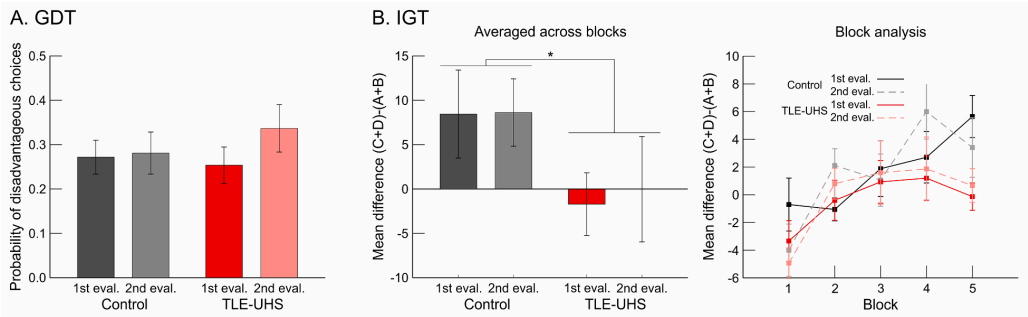

Fig. 2. A. Proportion of disadvantageous choices with reference to the total number of choices on the GDT for the mTLE-UHS group and control group at each evaluation. **B.** Frequency of advantageous (C + D) and disadvantageous selections (A + B) averaged across blocks during the IGT for the control and mTLE-UHS groups, at each evaluation. Error bars represent SEMs. **C.** Mean difference between the frequency of advantageous (C + D) and disadvantageous selections (A + B) at each block of the IGT for the control and mTLE-UHS groups, at each evaluation. Error bars represent SEMs.

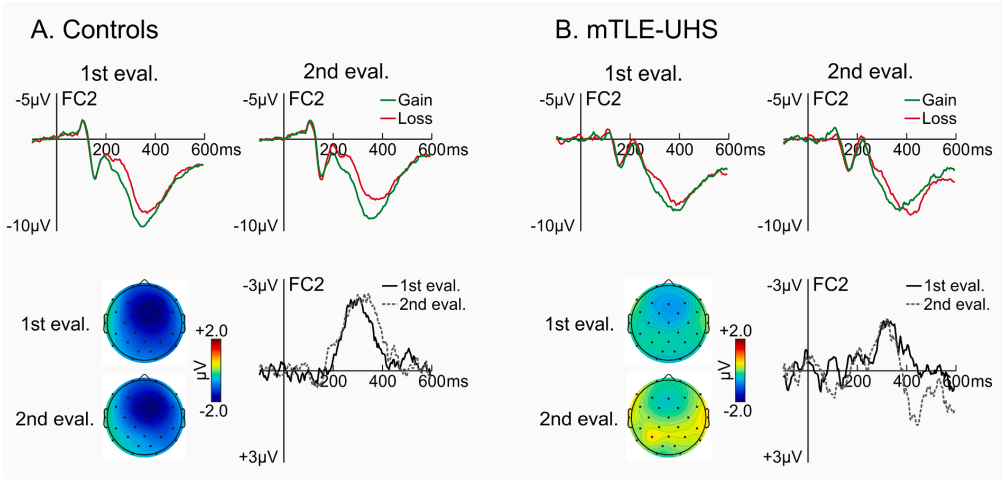

Fig. 3. Event-Related Potentials (ERPs) associated with feedbacks indicating monetary gains (solid black line) and losses (solid red line), and the differences between them (loss - gain; black pointed line) for each group (mTLE-UHS, controls) and evaluation (first, second), at FC2 electrode. Loss minus gain difference waveform at FC2 electrode for each group and evaluation (first, solid line; second, pointed line). **A.** For the control group, ERPs (top), difference waveform (bottom) and scalp topographical maps for the difference waveform (loss minus gain) between 250 and 350 ms. **B.** For the mTLE-UHS group, ERPs (top), difference waveform (bottom), and scalp topographical maps for the difference waveform (loss minus gain) between 250 and 350 ms.

Evaluation, $F(1,32) = 0.51$, $p = .481$].

No significant main effect of Group was encountered [$F(1,32) = 0.39$, $p = .536$]. Importantly, the significant interaction between Valence and Group suggest that there might be differences in the amplitude of the FRN (amplitude difference between gains and losses) between the mTLE-UHS and the control group [Valence × Group: $F(1,32) = 5.02$, $p = .032$]. In order to understand whether the group differences in the FRN amplitude were due to differences in the processing of gains or losses, pairwise *t*-test post-hoc comparisons were performed between groups. But, no significant group differences were observed in the mean amplitude of gains [$t(32) = 1.21$, $p = .235$] or losses [$t(32) = -0.047$, $p = .963$], and consequently it was not possible to disentangle whether this effect was specifically due to a stronger response to gains or to losses in either group. However, separately for each group, we performed paired *t*-test post-hoc comparisons between the mean amplitude of gains compared to the mean amplitude of losses, to test if the valence effect associated to the FRN was present in both groups. Interestingly, this contrast was significant in the control group [$t(16) = 3.22$, $p = .005$], but not in the TLE-UHS group [$t(16) = 1.98$, $p = .065$], suggesting that the valence effect, in other words the FRN, was present only in the control group (see Fig. 3 to visualize the FRN reduction in mTLE-UHS). Interestingly, FRN amplitude was not affected by surgery, as indicated by the non-significant Evaluation × Group [$F(1,32) = 0.19$, $p = .667$] and Valence × Evaluation × Group interactions [$F(1,32) = 0.31$, $p = .582$].

4.4. EROs analyses

Figs. 4–6 show the results of the oscillatory analysis for frequencies between 1 and 40 Hz, associated with gains and losses for the control and mTLE-UHS groups, respectively. A rmANOVA with two within-subjects factors: Valence (Gain, Loss) and Evaluation (First, Second), and one between-subjects factor (Group) was carried out for each frequency band.

Delta band. As expected based on previous literature, delta activity (3–4 Hz between 250 and 350 ms; Fig. 4) was higher for gain trials as compared to losses [main effect of Valence: $F(1,32) = 24.05$, $p < .001$]. No significant effects were observed between evaluations [main effect of Evaluation: $F(1,32) = 3.84$, $p = .059$; Valence × Evaluation: $F(1,32) = 0.02$, $p = .886$].

An overall reduction in delta power was observed in the TLE-UHS group as compared to the control group [Group: $F(1,32) = 7.73$, $p = .009$]. A significant Valence × Group interaction [$F(1,32) = 4.17$, $p = .049$] was observed. First, we performed pairwise *t*-test post-hoc comparisons between groups, which indicated that delta power was reduced in both conditions in the mTLE-UHS group in contrast to the control group [gains: $t(32) = 3.06$, $p = .004$; losses: $t(32) = 2.32$, $p = .027$]. Then, separately for each group, we carried out paired *t*-test post-hoc comparisons between the mean power of gains compared to the mean power of losses, to test whether the valence effect was present in both groups. Interestingly, and similarly to the results of the FRN, this contrast was significant in the control group [$t(16) = 5.06$, $p < .001$], but not in the TLE-UHS group [$t(16) = 1.967$, $p = .067$], which indicated that the valence effect was present only in the control group. Additionally, no significant differences were observed when comparing before and after surgery in patients with mTLE-UHS [Evaluation × Group: $F(1,32) = 2.31$, $p = .139$; Valence × Evaluation × Group: $F(1,32) = 0.16$, $p = .692$].

Theta band. For this oscillatory component (4–7 Hz, 200–400 ms; Fig. 5), a main effect of Valence was observed [$F(1,32) = 4.97$, $p = .033$], confirming the expected larger frontal theta activity after losses as compared to after gains. No significant differences were found between evaluations [main effect of Evaluation: $F(1,32) = 0.23$, $p = .635$; Valence × Evaluation: $F(1,32) = 0.19$, $p = .665$]. Importantly, the presence of a significant main effect of Group [$F(1,32) = 5.42$, $p = .026$], but the absence a of significant Group × Valence interaction [$F(1,32) = 0.52$, $p = .473$], suggested that the mean power of both gains and losses was reduced in the mTLE-UHS group compared to the control group. Moreover, these analyses corroborated that the difference in power between gains and losses (Valence effect) was similar between groups (see Fig. 5A and 5B). Interestingly, theta activity was not affected by surgery in mTLE-UHS [Evaluation × Group: $F(1,32) = 2.27$, $p = .141$; Valence × Evaluation × Group: $F(1,32) = 0.37$, $p = .546$].

Beta-gamma band. For this oscillatory component (27–32 Hz and 330–430 ms; Fig. 6), a significant main effect of Valence [$F(1,32) = 14.60$, $p < .001$] was encountered, corroborating that the frontal beta-gamma activity was increased for monetary gains as compared to monetary losses. No significant changes due to evaluation were found

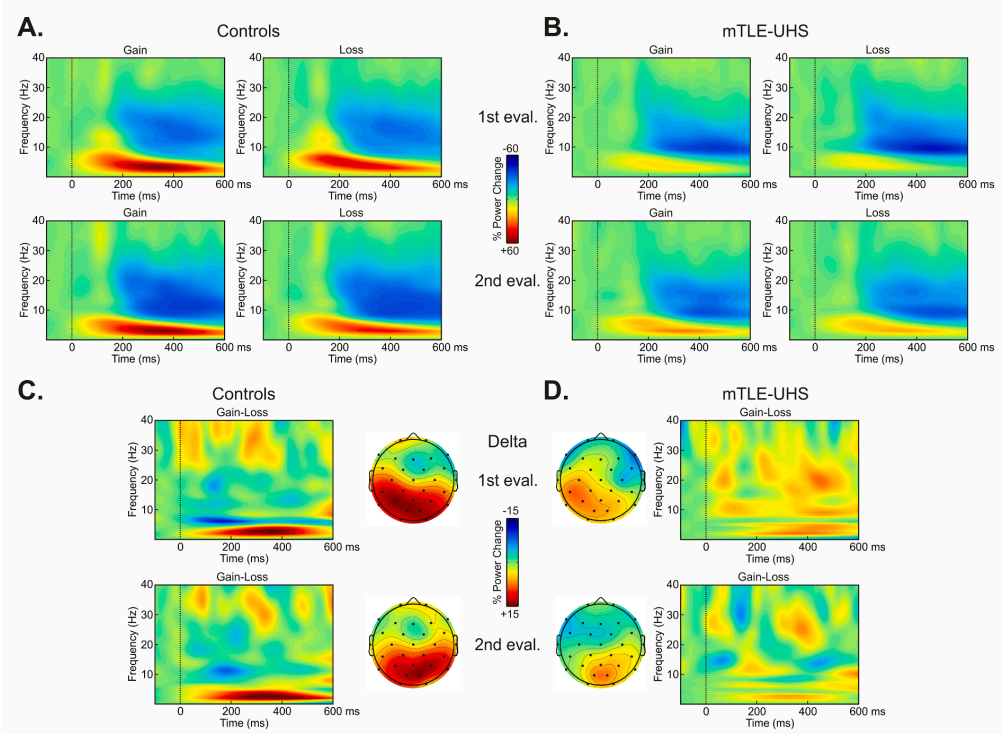

Fig. 4. Time–frequency plots representing power changes (with respect to the baseline) at frequencies between 1 and 40 Hz, at the selected ROI of electrodes (*P3*, PZ, *P4*, PO1, PO2). **A.** For the control group, time–frequency plots after gains (left) and after losses (right), for both first (top) and second (bottom) evaluations. **B.** For the mTLE-UHS group, time–frequency plots after gains (left) and after losses (right), for both first (top) and second (bottom) evaluations. **C.** For the control group, time–frequency plots with the differences between gains and losses and scalp distribution for the delta band-range (3–4 Hz, 250–350 ms), for both first (top) and second (bottom) evaluations. **D.** For the mTLE-UHS group, time–frequency plots with the differences between gains and losses and scalp distribution for the delta band-range (3–4 Hz, 250–350 ms), for both first (top) and second (bottom) evaluations.

[Evaluation: $F(1,32) = 1.09$, $p = .304$; Valence × Evaluation: $F(1,32) = 0.26$, $p = .614$]. No significant differences were observed across groups [$F(1,32) = 0.78$, $p = .385$; Valence and Group, $F(1,32) = 0.69$, $p = .412$]. Importantly, the surgery did not produce impairments in frontal beta-gamma activity in mTLE-UHS, as no significant interactions between Evaluation and Group were observed [Evaluation × Group: $F(1,32) = 0.21$, $p = .65$; Valence × Evaluation × Group: $F(1,32) = 0.06$, $p = .812$].

4.5. Correlation analyses

Correlation analyses were performed to test whether clinical variables in patients with mTLE-UHS (age at epilepsy onset, disease duration, and seizure frequency (days/month)) correlated with electrophysiological measures at the first evaluation (see Table 3). Please note that for this analysis, we only included the electrophysiological measures with significant group differences in previous analyses. Also, they were not corrected for multiple comparisons, specifically with regard to the amplitude of the FRN (loss minus gain), the mean frontal theta power (mean between gain and loss), the mean parietal delta power (mean between gain and loss), and the parietal delta power difference (gain minus loss). No statistically significant correlations were found, except for a significantly negative correlation between disease duration and parietal delta power difference.

5. Discussion

In the present study, we investigated decision-making and electrophysiological correlates of feedback processing in a group of patients with mTLE-UHS, before and after resective epilepsy surgery. We found that the mTLE-UHS group showed a riskier decision-making pattern on the IGT throughout the task, as compared to the control group. No significant group differences were found on the GDT or the probabilistic gambling task. Together with these behavioral findings, we also observed abnormal feedback processing in patients with mTLE-UHS as compared to controls, manifested by: (i) a decreased FRN, (ii) a weaker effect of emotional valence (loss vs monetary gains), together with a general reduction of the parietal delta activity, and (iii) a general reduction of frontal theta activity. Interestingly, patients also showed a normal effect of valence for the frontal theta activity and normal frontal beta-gamma activity. Importantly, in the mTLE-UHS group none of these measures significantly differed between the first and the second evaluation. These results indicate the presence of potential impairments in decision-making, specifically related to problems in feedback processing, suggesting that the malfunctioning reward system in patients with mTLE-UHS was already present, even before surgery.

5.1. Behavioral risk-related findings

In line with previous behavioral studies, we observed that under conditions of risk (evaluated with the GDT), patients with mTLE-UHS

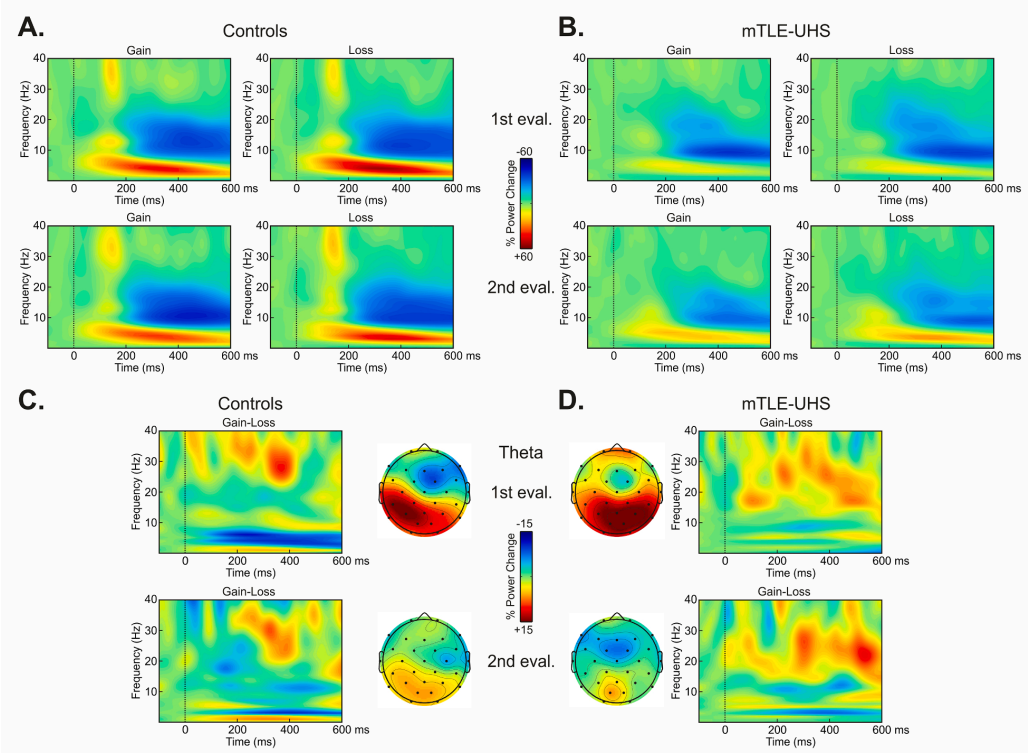

Fig. 5. Time–frequency plots representing power changes (with respect to the baseline) at frequencies between 1 and 40 Hz, at FC2 electrode. **A.** For the control group, time–frequency plots after gains (left) and after losses (right), for both first (top) and second (bottom) evaluations. **B.** For the mTLE-UHS group, time–frequency plots after gains (left) and after losses (right), for both first (top) and second (bottom) evaluations. **C.** For the control group, time–frequency plots with the differences between gains and losses and scalp distribution for the theta band-range (4–7 Hz, 200–400 ms), for both first (top) and second (bottom) evaluations. **D.** For the mTLE-UHS group, time–frequency plots with the differences between gains and losses and scalp distribution for the theta band-range (4–7 Hz, 200–400 ms), for both first (top) and second (bottom) evaluations.

performed just as well as the matched controls (Bonatti et al., 2009; Labudda et al., 2009; Delazer et al., 2010). However, under ambiguity or uncertain conditions (measured with IGT), patients showed substantial impairments in decision-making manifested through a greater number of disadvantageous/riskier card choices throughout the entire task. Interestingly, the statistical analysis corroborated the presence of impairments throughout the whole task. These findings partially align with previous research showing that patients with mTLE-UHS selected more disadvantageous cards than healthy controls (Labudda et al., 2009; Delazer et al., 2010; Yamano et al., 2011; Xie et al., 2013). This evidence may indicate difficulties in optimizing behavioral patterns based on feedback when there are only implicit rules and risky decisions should be avoided (for a review see Zhang et al., 2018), and might be linked to current electrophysiological findings. Moreover, we expected that the differences between groups would most likely occur towards the end of the IGT, when rules should be acquired, but patients might present learning difficulties. However, we were clearly unable to replicate the effect observed in past literature, as all the interactions involving group were not significant (suggesting similar learning between groups), which could probably be explained by our study's small sample size (see Limitations section for more information). It is also important to mention that no significant behavioral differences were observed between patients with mTLE-UHS and healthy controls on the ERP probabilistic gambling task. These results are in line with previous studies observing significant differences between diverse clinical groups and healthy controls at the electrophysiological level but not at the behavioral level (e.g., Miedl et al., 2014; Gomez-Andres et al., 2019; Stewart et al., 2019), which would suggest the task's lack of sensitivity in capturing behaviorally subtle clinical differences (Lin et al., 2013). Another possible explanation for these results is the reduced sensitivity to detect subtle behavioral effects due to the small sample size of each group (see Limitations section as well). Therefore, it remains necessary for future studies to carry out behavioral validation of this task and other related ones.

5.2. *Electrophysiological findings*

The typical electrophysiological pattern of feedback processing was observed on our probabilistic gambling task, consisting of a clear frontocentral FRN, greater parietal delta and frontal beta-gamma activities after gains, as compared to losses, and increased frontal theta activity after losses, as compared to after gains (Gehring and Willoughby, 2002; Cohen et al., 2007; Trujillo and Allen, 2007; Marco-Pallares et al., 2008; Cavanagh et al., 2010; Bernat et al., 2011; Foti et al., 2015; Williams et al., 2021).

Concerning group effects, we found a reduced FRN (difference waveform) in patients with mTLE-UHS as compared to controls, corroborated by the significant interaction between valence and group. To better delineate the cognitive processes involved in this effect, we decomposed the FRN component into the time–frequency domain, and

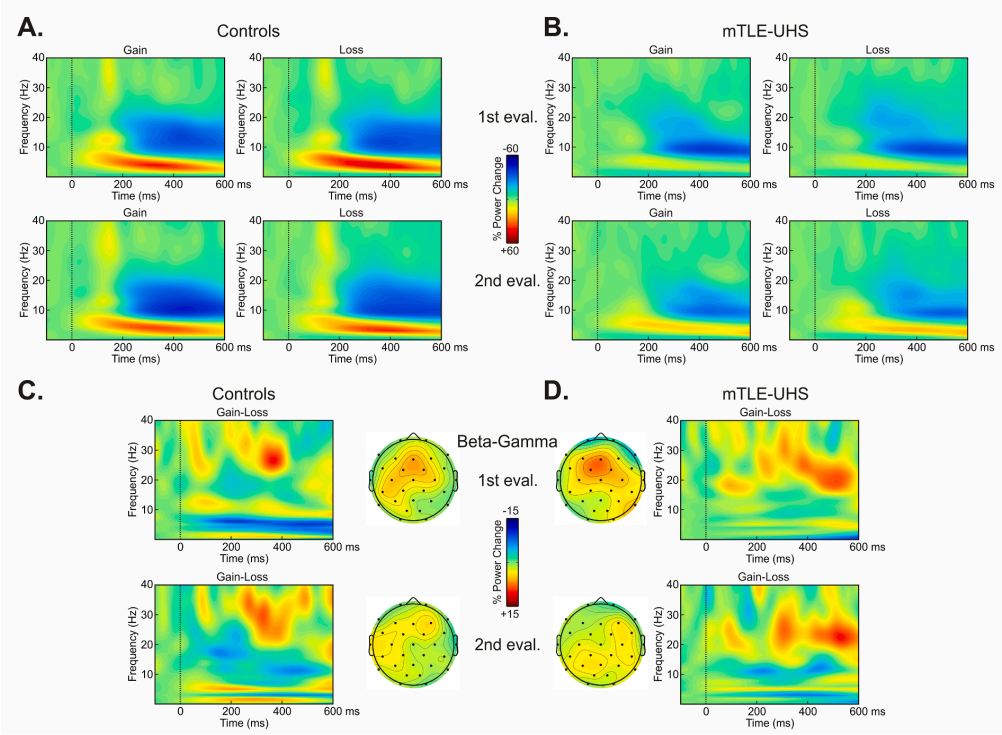

Fig. 6. Time–frequency plots representing power changes at frequencies (with respect to the baseline) between 1 and 40 Hz, at the selected ROI of electrodes (F3, FZ, F4, FC1, FC2). **A.** For the control group, time–frequency plots after gains (left) and after losses (right), for both first (top) and second (bottom) evaluations. **B.** For the mTLE-UHS group, time–frequency plots after gains (left) and after losses (right), for both first (top) and second (bottom) evaluations. **C.** For the control group, time–frequency plots with the differences between gains and losses and scalp distribution for the beta-gamma band-range (27–32 Hz and 330–430 ms), for first (top) and second (bottom) evaluations. **D.** For the mTLE-UHS group, time–frequency plots with the differences between gains and losses and scalp distribution for the beta-gamma band-range (27–32 Hz and 330–430 ms), for both first (top) and second (bottom) evaluations.

Table 3
For patients with mTLE-UHS, Pearson correlations between age at epilepsy onset (Onset), disease duration (Dis. Duration), seizure frequency in days/month (Frequency), and electrophysiological measures at the first evaluation, including the amplitude of the FRN (loss minus gain), delta power difference (gain minus loss), mean theta power (mean between gain and loss), and mean delta power (mean between gain and loss) were executed.

	FRN	Delta Difference	Mean Delta	Mean Theta
Onset	−0.021	0.034 (0.896)	0.037	0.092
	(0.935)		(0.889)	(0.727)
Dis.	0.184	**−0.506**	−0.269	−0.345
Duration	(0.480)	**(0.038)**	(0.296)	(0.175)
Frequency	0.156	−0.155	−0.194	−0.252
	(0.550)	(0.552)	(0.456)	(0.329)

P-values were not corrected for multiple comparisons.

focused on its main oscillatory generators, the parietal delta and frontal theta activities (Cohen et al., 2007; Trujillo and Allen, 2007; Marco-Pallares et al., 2008; Cavanagh et al., 2010; Williams et al., 2021).

The contribution of the parietal delta activity to the FRN, mostly related with the processing of positive feedbacks, has been suggested to represent a neural index of expectancy-sensitivity (Watts et al., 2017), critical to feedback learning and choice or action selection (Cavanagh et al., 2012; Walsh and Anderson, 2012). The weaker effect of valence on parietal delta power, together with a general reduction of power in this frequency range, in the mTLE-UHS group as compared to the control group, might explain the reduced FRN and associated impairments in feedback processing. Furthermore, these results might suggest that patients with mTLE-UHS have difficulty correctly evaluating external outcomes. Moreover, this could affect the patients' capacity to make accurate predictions about future outcomes, which might explain the problems associated to riskier or impulsive behaviors in this population, on ambiguous or uncertain decision-making tasks (Labudda et al., 2009; Yamano et al., 2011; Xie et al., 2013; Zhang et al., 2018).

Frontal theta activity also contributes to the FRN, specifically by processing negative feedbacks, and has been related to cognitive monitoring and reinforcement learning, as well as indexing the need to readjust behavior and deviations from the predicted value of the actions (Cavanagh et al., 2012; Janssen et al., 2016). However, given that we did not observe a weaker effect of valence on theta power, these processes might be preserved in patients with mTLE-UHS, and the reduced FRN in this group, might not be related to theta activity. Interestingly, the total theta power is also related to other processes different from the ones related to the FRN (Rawls et al., 2020). In light of this, the general reduction of theta power observed in patients with mTLE-UHS in contrast to healthy controls, might be related to problems with encoding task-relevant information (Siegle and Wilson, 2014; Kerrén et al., 2018; Sugar and Moser, 2019).

Additionally, and despite a visual inspection of Fig. 6 potentially suggesting the contrary, we did not observe statistically significant differences between groups in frontal beta-gamma activity. This frequency

range has been suggested to be a neural marker of reward processing associated with monetary gains (Marco-Pallares et al., 2008; Marco-Pallarés et al., 2009), positive feedback, and prediction errors (Cohen et al., 2007; Cunillera et al., 2012; HajiHosseini et al., 2012). Importantly, it has also been related to expectancy mechanisms (HajiHosseini et al., 2012), and associated to information processing integration of remote structures (Buzsáki and Draguhn, 2004). Taking into account results of frontal beta-gamma activity, these processes may be preserved in patients with mTLE-UHS.

5.3. Network disorganization in mTLE-UHS

Although the focus of damage in patients with mTLE-UHS is the hippocampus, neuroimaging studies have observed that this disorder causes progressive damage and neural reorganization in regions and networks connected with the mesial temporal lobe (Spencer et al., 2002; Maller et al., 2019; Roger et al., 2020; Morgan et al., 2021). Importantly, some of these networks may have a clear role in feedback processing and decision-making (Martínez-Selva et al., 2006), but also in working memory, episodic memory, language, verbal comprehension, processing speed, and constructional abilities (Zhang et al., 2018; Reyes et al., 2019; Ives-Deliperi and Butler, 2021). For this reason, the current findings provide important insights about which brain networks might be affected in mTLE-UHS.

Along these lines, it has been suggested that the processes related to the generation of the delta activity associated to the FRN were supported by connections between the ventral striatum and other subcortical regions linked to the mesial temporal cortex (Foti et al., 2015). Importantly, the disorganization of this network in mTLE-UHS, may have a clear impact on impairing the proper processing of feedbacks, diminishing the delta power and FRN amplitude, and affecting the selection of choices (Cavanagh et al., 2012; Walsh and Anderson, 2012) during decision-making, at least, under ambiguity (IGT). Additionally, the negative correlation found between disease duration and delta power difference, may add additional support in understanding how progress in network disorganization might generate progressive impairment of these processes.

In contrast, the frontal theta activity linked to the FRN relies more on networks connected with the anterior cingulate cortex. This activity has been suggested to reflect the influence of a decrease in ventral tegmental area dopaminergic signals in the midbrain after unexpected punishments, which is transmitted to the medial prefrontal cortex (mPFC), especially the anterior cingulate cortex (Holroyd and Coles, 2002; Nieuwenhuis et al., 2004; Müller et al., 2005). This signal is related with mediating subsequent behavioral adjustments (Cohen et al., 2007; Marco-Pallares et al., 2008; Foti et al., 2015). Interestingly, these processes were not significantly affected in our sample of patients with mTLE-UHS, suggesting a functional preservation of the anterior cingulate cortex network (Morgan et al., 2021).

However, we observed a clear reduction in total frontal theta power in the mTLE-UHS group as compared to the control group. The amount of theta power has been strongly associated with the hippocampus, but also with the mesial temporal regions in general, and has been linked to cognitive control, computational processes (Buzsáki, 2002), and importantly working-memory and memory encoding (verbal and visuospatial) (Brzezicka et al., 2019). Thus, the reduction in theta activity observed in patients with mTLE-UHS, might also reflect a dysfunction of active information maintenance, but also encoding abilities, as well as difficulties in learning from feedbacks in uncertain and ambiguous situations due to the inability to create expectations across the task (Vilà-Balló et al., 2017). Importantly, the mesial temporal network supporting these processes is one of the first being affected in patients with mTLE-UHS (Li et al., 2015).

Taking together behavioral, electrophysiological, and neuropsychological findings, it is possible to suggest that a relative preservation of the cognitive route, despite a disruption in the emotional route (Bonatti et al., 2009; Delazer et al., 2010) might also explain why patients with mTLE-UHS did not present significant impairments in decision-making under risk. However, the disruption of feedback processing (emotional route), together with the difficulties in working memory and memory, might explain the poor performance shown by patients with mTLE-UHS when performing decision-making under ambiguity (Martínez-Selva et al., 2006; Toplak et al., 2010; Yamano et al., 2011; Von Siebenthal et al., 2017). Interestingly, the disruption of mesial temporal lobe networks, with a special emphasis on the hippocampus, may partially explain these impairments (Stretton and Thompson, 2012). However, it is also important to mention that the abnormalities in other brain networks, such as fronto-parietal networks, mostly related with working memory and memory, might participate in the observed impairments in mTLE-UHS (Stretton and Thompson, 2012; Campo et al., 2013; Enatsu et al., 2015). In this vein, reduced activations of the superior parietal lobe have been observed in mTLE-UHS patients compared to healthy controls during working-memory tasks (Stretton and Thompson, 2012; Caciagli and Bassett, 2022). In this line, other studies detected stronger functional connectivity between this region (Stretton et al., 2013) and the hippocampus ipsilateral to the lesion (Stretton et al., 2014) in mTLE-UHS as compared to controls.

When focusing on the other neuropsychological results, deficits in verbal comprehension in patients with mTLE-UHS were in line with previous results (Yang et al., 2016; Zhang et al., 2018; Reyes et al., 2019; Ives-Deliperi and Butler, 2021) on left hemisphere lesions. In this line, although we expected to find alterations in verbal functioning due to the presence of patients with left temporal lobe lesions, in this study the impact on verbal functioning (measured through the BNT and verbal and semantic fluency tasks) did not reach significance. Furthermore, no significant impairments were detected for constructional abilities, fitting with previous studies indicating that the visuospatial domain is rarely impaired in patients with mTLE-UHS (Lee et al., 2002; Tallarita et al., 2019). Interestingly, speed processing deficits have been encountered in some patients with mTLE-UHS. Here, we did not observe significant impairments to this function. This would simply suggest that our sample mostly fits with the memory profile described by Reyes et al. (2019, 2020), despite certain deficits in verbal functioning.

5.4. Post-surgical effects

The resection of the anterior mesial temporal lobe for the relief of medically intractable mTLE-UHS constitutes the disconnection of this pathological network. But, surgery usually generates additional impairments (Zhang et al., 2018) such as in naming (Hermann et al., 1994; Sherman et al., 2011; Ives-Deliperi and Butler, 2012; Busch et al., 2016, 2018), and verbal memory (Hamberger and Drake, 2006). Taking into account these studies, but also the link between mesial temporal lobe networks and reward processing (Vilà-Balló et al., 2017) and decision-making (Bonatti et al., 2009; Labudda et al., 2009; Delazer et al., 2010; Yamano et al., 2011; Xie et al., 2013; Von Siebenthal et al., 2017), we initially expected additional impairments in these processes in patients with mTLE-UHS after surgery (Zhang et al., 2018). However, contrary to our initial hypothesis, we did not find differences between the first and second evaluations in patients with mTLE-UHS at both behavioral and electrophysiological levels, which might indicate that: (i) the emotional route (related with the IGT, Delazer et al., 2010), more dependent on ventral striatum and mesial temporal cortex connections (Foti et al., 2015), was already disrupted prior to surgery; whereas (ii) the cognitive route (related with the GDT, Delazer et al., 2010), which might rely on large-scale networks, may not have been directly affected by the resection of mesial-anterior temporal areas. Moreover, the surgery affected cognitive functioning in patients with mTLE-UHS, as seen by a decrease in verbal functioning and verbal memory scores from the first to the second evaluation. These results fit with previous literature, indicating that it is common to have a reduction of verbal function particularly related to naming (Hermann et al., 1994; Sherman et al.,

2011; Ives-Deliperi and Butler, 2012; Busch et al., 2016, 2018), and verbal memory function, after the surgery (Hamberger and Drake, 2006), due to the resection of mesial temporal structures of the critical left brain networks involved in these processes.

6. Limitations

This study is not free of limitations. The first limitation is related to the small sample size of the mTLE-UHS group, which may explain the lack of a significant Block × Group interaction on the IGT and also the lack of group differences in the ERP probabilistic gambling task. Consequently, only a partial replication of previous results (Labudda et al., 2009; Delazer et al., 2010; Yamano et al., 2011; Xie et al., 2013) occurred, and generalization of these results should be done with caution. Similarly, the small sample size did not permit us to separate patients into the four profiles defined by (Reyes et al., 2019). For this reason, generalization of these results to other mTLE-UHS profiles (Reyes et al., 2019), less affected by memory impairments, should be done with prudence. The second limitation is related to the fact that the same neuropsychological tests were used for both evaluations and this may result in increased performance due to practice. In fact, the time elapsed between the two evaluations (6 months) may not be sufficient to prevent certain practice effects on neuropsychological evaluations, which have been found, in some studies, to persist for years (Grunwald et al., 1998; Basso et al., 1999; Salthouse and Tucker-Drob, 2008; Helmstaedter et al., 2020). However, in the present study, controls exhibited a practice effect (performance improvements on some measures), whereas patients did not improve on any of the measures and even showed a decline in performance, in some cases. This pattern suggests that the deterioration of verbal functioning and verbal memory, observed in patients after surgery, may have been even more pronounced if different versions of the same tests were used between evaluations. Third, despite some findings indicating that altered reward processing may be associated with the depressive symptomology, frequently observed in patients with mTLE-UHS (Kondziella et al., 2007; Keren et al., 2018; Mikulecká et al., 2019), we did not perform an adequate evaluation of psychiatric symptoms. For this reason, we were unable to infer how the presence of negative emotional states in our population could affect the present results. Further studies are needed to confirm the impairments in feedback processing observed in the current study, but also to disentangle the relationship between cognitive impairments and mTLE-UHS profiles, negative emotional states, decision-making, and the network involved in mTLE-UHS (Camara et al., 2009; Haber and Knutson, 2010; Vilà-Balló et al., 2017).

7. Conclusion

The present investigation is the first study that assesses decision-making and electrophysiological correlates of feedback processing in patients with mTLE-UHS and monitors these processes before and after the epilepsy surgery. Our results suggest that patients with mTLE-UHS have impairments in decision-making under ambiguity, when they need to make decisions using the information provided by the outcomes, but not in decision-making under risk. Additionally, no differences were found between patients and controls when the task does not have any structure and feedbacks are random. These findings may be explained by an abnormal feedback processing detected with the altered EEG activity patterns, and likely boosted by the concomitant alterations in working memory, and in visuospatial and verbal memory. Taken together, these dysfunctions may make it more difficult to generate correct expectations of the outcomes, and therefore to adaptively make decisions. Importantly, these impairments might be the consequence of the disruption of brain networks connected to the mesial temporal lobe. Furthermore, the observed impairments in feedback processing and decision-making under ambiguity were already affected in patients with mTLE-UHS before surgery, and did not significantly worsen after surgery.

CRediT authorship contribution statement

Adrià Vilà-Balló: Conceptualization, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Myriam De la Cruz-Puebla:** Investigation, Validation, Writing – original draft, Writing – review & editing, Visualization. **Diana López-Barroso:** Investigation, Writing – review & editing, Supervision. **Júlia Miró:** Resources, Investigation, Writing – review & editing. **Jacint Sala-Padró:** Resources, Investigation. **David Cucurell:** Methodology, Software, Data curation, Writing – review & editing. **Mercè Falip:** Resources, Writing – review & editing, Funding acquisition. **Antoni Rodríguez-Fornells:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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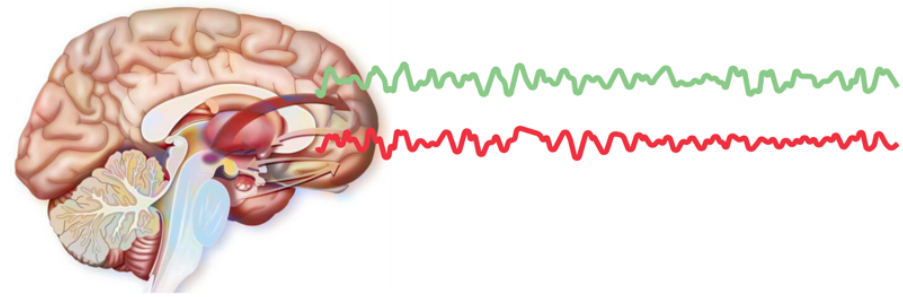

CHAPTER III: fMRI CORRELATES OF REWARD PROCESSING IN MTLE-UHS PATIENTS

Reward Circuitry functioning in Mesial Temporal Lobe Epilepsy: Insights from fMRI before and after Surgery

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Keywords: Mesial Temporal Lobe Epilepsy, Unilateral Hippocampal Sclerosis, Epilepsy surgery, Reward processing, Decision-making.

ABSTRACT

Objective: This study examined the neural correlates of reward processing (RP) in patients with mesial Temporal Lobe Epilepsy due to Unilateral Hippocampal Sclerosis (mTLE-UHS) before and after epilepsy surgery using fMRI and a probabilistic gambling task (PMGT). **Methods:** Twenty-eight mTLE-UHS patients and 20 healthy controls underwent fMRI scans pre-surgically and post-surgically (for patients) or longitudinally (for controls). **Results:** Pre-surgically, mTLE-UHS patients compared to healthy controls exhibited reduced activity in the unaffected hemisphere (UH) amygdala-insula-superior temporal gyrus and dorsolateral prefrontal cortex during both gain and loss processing. The affected hemisphere (AH) superior frontal gyrus showed reduced activity during loss processing. Post-surgically, a significant group-by-evaluation interaction was observed in both gain and loss conditions within the AH and the UH. Post-hoc analyses revealed significantly higher neural activation in the mTLE-UHS group compared to controls, regardless of the outcome's valence. No significant behavioral differences were observed between groups or sessions. **Conclusion:** Our findings suggest that mTLE-UHS is associated with altered brain activation patterns in reward-related circuitry, both before and after epilepsy surgery. Post-surgical changes, primarily in the AH, might reflect compensatory mechanisms, neuroplastic reorganization, or pre-existing disease-related neuroplasticity. The discrepancy between neural and behavioral findings highlights the need for further research into the complex interplay between neural alterations and behavioral outcomes in mTLE-UHS. Understanding the long-term impact of these changes on cognitive function, emotional regulation, and overall well-being is crucial for developing targeted interventions.

Keywords: mTLE-UHS, reward processing, decision-making, fMRI, epilepsy surgery, neuroplasticity, contralateral effects

1. INTRODUCTION

Every decision, trivial or momentous, hinges on our brain's assessment of potential positive (rewards) and negative (punishment) consequences (Lee, 2013; Lake et al., 2019, 2019). The neural substrates underlying decision-making and reward processing (RP) extend across vast cerebral regions (McClure et al., 2004; Hampton and O'doherty, 2007; Lee, 2013), with the dopamine-driven reward system being the cornerstone (Ferreri et al., 2021; Fung et al., 2021; Hahn et al., 2021; Peters et al., 2021). This system not only orchestrates our experiences of pleasure and motivation (Baik, 2021; Gold et al., 2023) but also shapes our behavior in response to rewards (Baik, 2020). This includes fundamental drives like the pursuit of food (Baik, 2021) and engagement in social interactions (Baker et al., 2020). Notably, the prefrontal cortex (PFC), specifically the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex, along with the ventral tegmental area (VTA), ventral medial and dorsolateral striatum (including the nucleus accumbens), and both the anterior and posterior cingulate cortex are central regions of the reward processing network (RPN) (Camara et al…. McClure et al., 2004; Marco-Pallares et al., 2008; Wang, 2012; Hiser and Koenigs, 2018; Cox and Witten, 2019; Lewis et al., 2021; Ogawa et al., 2022; Li et al., 2023; Rehbein et al., 2023; Rolls, 2023). Besides, extensive functional and structural connectivity exist between the RPN and mesial structures such as the hippocampus and the amygdala (Murray, 2007; Liu et al., 2011; Manssuer et al., 2022). Within this complex network, the PFC evaluates potential outcomes, guiding decision-making (Zoh et al., 2022). The ventral striatum/nucleus accumbens (NAcc), plays a key role in processing reward anticipation and motivation, driving goal-directed behavior (Delgado, 2007; Knutson and Greer, 2008). The anterior cingulate cortex (ACC) is involved in monitoring actions and outcomes, regulating cognitive control, and resolving conflict during decision-making (Rolls, 2019).

Meanwhile, the hippocampus associates external stimuli with reward outcomes (Sadler et al., 2020), and the amygdala assigns emotional significance to these associations (Perlman et al., 2012), being both regions essential for upregulating learning. Compromised neural integrity, especially within mesial brain structures, has the potential to significantly affect decision-making and learning pathways. This may manifest as a propensity for impulsive behavior and a greater inclination towards risk-taking. Furthermore, alterations in reward sensitivity may arise, suggesting modifications in RP mechanisms (Sailer et al., 2008; Bunzeck et al., 2012)

Following this line of thinking, Mesial Temporal Lobe Epilepsy due to Unilateral Hippocampal Sclerosis (mTLE-UHS) is a neurological condition characterized by chronic dysfunction of mesial temporal structures, including the hippocampus, often accompanied by amygdala alterations (Bunzeck et al., 2012; Manmatharayan et al., 2023). The structural anomalies found in mesial temporal lobe epilepsy (mTLE) patients are frequently associated with cognitive and emotional deficits (Fang et al., 2017; Reppert et al., 2023; Witt et al., 2023). Importantly, one-third of individuals with mTLE associated to hippocampal sclerosis (HS) develop drug-resistant epilepsy (Vega-García et al., 2022). Surgical resection of the epileptogenic focus, such as anterior temporal lobectomy, has proven efficacious in many cases, significantly reducing seizures and improving quality of life (Wiebe et al., 2001; Usui, 2016; Yue et al., 2020; Lu et al., 2023). Clinically, patients with mTLE often present with depression and anhedonia as frequent comorbidities (Lothe et al., 2008; Hennion et al., 2015), potentially linked to dysfunction in the reward system.

Previous research has explored the intricate relationship between mTLE and impairments in decision-making and feedback processing. Specifically, several investigations (see

Butman et al., 2007; Bonatti et al., 2009; Labudda et al., 2009; and Delazer et al., 2010) have consistently demonstrated that individuals with mTLE exhibit a propensity for riskier choices compared to healthy controls, particularly evident in tasks like the Iowa Gambling Task (IGT). This suggests a potential dysfunction within the neural circuitry responsible for evaluating rewards and punishments, leading to suboptimal decision-making and learning patterns. Regarding, the effects of epilepsy surgery, pre-surgical investigations suggest that mTLE patients often exhibit impairments in decision-making under ambiguity, where no explicit information about the consequences of each decision is given, which is also associated with selective reductions in executive function and earlier seizure onset (Labudda et al., 2009). Notably, even patients with HS, without amygdala involvement, demonstrate tendencies towards disadvantageous decision-making (Labudda et al., 2009; Delazer et al., 2010). Post-surgery, challenges persist in decision-making under ambiguity, highlighting persistent cognitive deficits despite intervention (Bonatti et al., 2009). Furthermore, the investigation into the electrophysiological correlates of feedback processing performed by (Vilà-Balló et al., 2022) have revealed in mTLE-UHS patients a disruption of the Feedback-Related Negativity (FRN) component, which is typically associated with negative feedback and learning from errors. Additionally, a diminished differentiation in brain activity between positive and negative feedback, coupled with reduced parietal delta and frontal theta activity, points towards a compromised ability to process and utilize feedback information effectively. Interestingly, despite these impairments, mTLE-UHS patients have exhibited a preserved valence effect for frontal theta activity and normal frontal beta-gamma activity (Vilà-Balló et al., 2022). This suggests that while certain aspects of feedback processing are demonstrably affected, other components of the reward system may remain relatively intact. Critically, these findings appear to be present even before

epilepsy surgery and do not show significant changes post-surgery. This implies that the underlying neural dysfunction may be a consequence of the disease process itself rather than a result of surgical intervention.

Further investigation of the reward system in mTLE using resting-state fMRI such as the conducted by Cataldi and colleagues (2013), have revealed alterations in the connectivity and activity of key brain networks. Specifically, abnormal connectivity patterns within the default mode network, attention network, and reward/emotion network, have being shown, providing a potential neural basis for the cognitive and affective disturbances observed in mTLE patients (Cataldi et al., 2013). Additionally, graph theoretical analysis has revealed disruptions in the topological organization of brain networks in mTLE, including the reward system, with differences observed between left and right temporal lobe epilepsy (TLE) (Ma et al., 2023). These findings highlight the widespread impact of mTLE on brain function, extending beyond the seizure focus. Also, Simultaneous EEG-fMRI studies have shed light on the dynamic effects of interictal epileptiform discharges (IEDs) on the reward system. Specifically, the research performed by Tong and colleagues (2019) has shown that IEDs originating from the left temporal lobe primarily impact the hippocampus and its connections with the default mode network, while also influencing the reward-emotion network. In contrast, right temporal lobe IEDs appear to have a greater influence on the amygdala and its associated networks, including also the reward system. These findings suggest that IEDs can disrupt the normal functioning of the reward circuitry, potentially contributing to the observed impairments in RP and decision-making in mTLE patients (Tong et al., 2019).

While fMRI studies have explored the effects of mesial temporal lobe epilepsy (mTLE) on RP in various contexts, research focusing specifically on patients with strictly

unilateral lesions associated with hippocampal sclerosis remains limited. This specific population presents a unique challenge in understanding the complex interplay between structural alterations, neural network dysfunction, and cognitive and emotional outcomes. Further research investigating the neural correlates of reward processing in this population is critical to understand the specific challenges faced by mTLE-UHS patients and to develop more targeted interventions

To bridge this gap, we aimed to investigate the correlates of RP in mTLE-UHS using fMRI techniques and using a Probabilistic Gambling Task. The fMRI data was acquired at two time points: longitudinally for the control group and pre- and post-epilepsy surgery for mTLE-UHS participants. Building upon previous evidence, we hypothesized that patients with mTLE-UHS who undergo surgical intervention will exhibit abnormal brain activation patterns within the RP circuitry, and potentially, the surgical resection of the epileptogenic tissue might result in changes in reward-related activations compared to pre-surgical evaluations. This research aims to offer valuable insights into the impact of mTLE and the epilepsy surgery on RP circuitry in mTLE-UHS patients.

2. METHOD

2.1. Participants

We performed a prospective observational study of a cohort of patients undergoing epilepsy surgery within the Bellvitge Hospital surgical program. Our study included 28 patients diagnosed with drug-resistant mTLE-UHS prior to surgery (first evaluation), who underwent both neuroimaging and neurological assessments. Additionally, we included 20 healthy individuals matched for age (Patients: 42.0 ± 11.7; Controls: 41.6 ± 14.6; t (46) = 0.110, p = 0.913), gender (Patients: 15 females, 13 males; Controls: 11 females, 9

males; χ^2 (1, N = 48) = 0.000, p = 1.000), years of education (Patients: 12.0 ± 3.7; Controls: 11.3 ± 4.2; t(46) = 0.595, p = 0.555) as is represented in Figure 1 A,B and C. None of the participants had a history of psychiatric disorders.

For the mTLE-UHS group, diagnostic confirmation involved clinical EEG, MRI findings, and comprehensive neurological and neuropsychological evaluations, supplemented by continuous video-EEG monitoring. To ensure research integrity, participants who experienced seizures within 24 hours before or during the study were excluded. All participants maintained a stable antiseizure medication regimen throughout the study period. Participants' sociodemographic and clinical data are detailed in Table 1.

In addition to the initial preoperative assessment (first evaluation), 24 mTLE-UHS patients also received a neuroimaging assessment after surgery (second evaluation). A subset of patients was excluded for not completing the post-operative neuroimaging evaluation (See Figure 2). All patients underwent anterior temporal resection performed by the same surgeon, and anatomopathological analysis was carried out by a single pathologist at our center. In the control group, 20 participants were also evaluated during their second visit at list six months follow-up. The methodology for participant selection is detailed in Figure 2. This study received full approval from the Ethical Committee of Bellvitge University Hospital (Approval No. PR064/10), and informed consent was obtained from all participants, ensuring compliance with ethical research standards.

2.2. MRI protocol

All participants underwent first and second whole-brain structural and functional MRI scans using a 3.0 Tesla Siemens Trio MRI scanner equipped with a 32-channel phased-

array head coil system. High-resolution T1-weighted structural images were acquired using a magnetization-prepared rapid-acquired gradient echo sequence (MPRAGE; slice thickness = 1mm; no gap; number of slices = 240; TR = 2300 ms, TE = 3 ms, matrix = 256x256; FOV = 244mm; voxel size 1x1x1mm).

For the reward-related gambling task, functional MRI data were collected using a single-shot T2*-weighted gradient-echo echo-planar imaging (EPI) sequence (slice thickness = 4 mm; no gap; number of slices = 32, interleaved order; TR = 2000 ms; TE = 29 ms; flip angle = 80°; matrix = 80 x 80; voxel size = 3 x 3 x 4 mm3, in three runs with 383 volumes by each run), covering all but the most superior region of the brain and the cerebellum. Visual stimuli were back-projected onto a screen using an LED projector, viewed through a mirror attached to the head coil, and responses were collected via magnet-compatible buttons.

2.3. Experimental Design

Probabilistic Gambling Task

In this study, we used a modified probabilistic gambling task to evaluate RP using a functional magnetic resonance imaging (fMRI) paradigm (Camara et al., 2008; Riba et al., 2008; Vaquero et al., 2017). Each trial began with an 8000 ms presentation of a fixation cross ('+'). Subsequently, participants were presented with a visual display containing two numerical options, 25 and 5, in one of two possible configurations: [25 5] or [5 25]. Participants were instructed to make a choice by pressing a corresponding button using their left or right index finger. For example, in the case of a [25 5] display, pressing the left button indicated selection of the number 25, while pressing the right button indicated selection of the number 5. Following the decision phase, a fixed interval

of 1500 ms elapsed, after which both numbers changed color. One turned red and the other turned green. If the number on the selected side turned red, it signified a monetary loss in the equivalent virtual Euro cents. Conversely, if the number on the selected side turned green, it indicated a gain. Four distinct standard feedback types were presented randomly: [**25** 5], [25 **5**], [5 **25**], and [**5** 25], where non-bold font represented red (loss) and bold font represented green (gain), accounting for 80% of trials. Additionally, unexpected bonus feedbacks were included [**125** 5], [25 **125**], [125 **25**], and [**5** 125], comprising 20% of the trials. The feedback stimulus lasted 8000 ms before transitioning to the subsequent trial. The experiment consisted of three separate runs, with each comprising 60 trials, for a total of 180 trials across the experiment. The proportion of standard and unexpected feedbacks was the same in each run. Furthermore, the expected value of monetary outcomes remained balanced within each run to minimize the influence of differential probabilities on decision-making. Participants were instructed to maximize their earnings. They began each session with 1000 points and were informed of their cumulative earnings at the end of each run. This approach ensured that participants were motivated to make choices that would increase their ear, while minimizing the potential influence of immediate feedback on their decisions. The total task duration was 63 minutes. This task was administered during fMRI scanning to investigate neural correlates of RP, as depicted in Figures 3A and 3B.

2.4. Data preprocessing

The fMRI data underwent a series of preprocessing steps utilizing the established protocols within the Statistical Parameter Mapping framework (SPM12, http://www.fil.ion.ucl.ac.uk/spm). After slice-timing correction to correct for the time difference between brain slice acquisitions, functional images were co-registered via an

affine rigid-body transformation with the first brain volume as reference to correct for head motion. Spatial transformations were computed to co-register anatomical and functional volumes and to wrap these into the standard Montreal Neurological Institute (MNI) space. Finally, functional images were smoothed utilizing an isotropic Gaussian Kernel with an 8-mm full-width at half-maximum to minimize effects of inter-subject anatomical differences.

Additionally, to standardize the lateralization of the affected hemisphere and facilitate comparative analysis, we aligned the images of mTLE-UHS patients according to the location of the epileptogenic focus. This alignment enabled direct comparison between the ipsilateral (affected) and contralateral (unaffected) mTLE regions. Specifically, images of patients with a right-sided focus were flipped to align all lesions to the left hemisphere. Correspondingly, an equal number of control group images were mirrored to ensure consistent comparison.

2.5. Procedure

In our research, we implemented a longitudinal framework, consisting of two distinct assessment phases. The initial phase served as the baseline assessment, while the subsequent phase, conducted as a follow-up, was systematically scheduled with a minimum interval of six months from the baseline for the control group. This interval aimed to mitigate any potential effects of learning or familiarity with the testing procedure.

For the patient cohort with mTLE-UHS, the follow-up phase was specifically positioned in the postoperative timeline, ensuring that at least three months had passed since their surgical intervention for epilepsy. This temporal arrangement enabled us to capture

potential brain reorganization attributable to the surgery. In this paper, we will refer to these phases as the 'first evaluation' and the 'second evaluation,' with the first evaluation establishing a pre-surgical baseline and the second evaluation providing insights into the post-surgical cognitive landscape.

2.6. Statistical analysis

Due to some participants not completing the post-surgical evaluations, as detailed in the Participants section, the sample size differed between the first and second evaluations. Consequently, we first evaluated the effects on RP related to mTLE-UHS using the initial cohort from the first evaluation. Then, we assessed the postsurgical effects by comparing the first and second follow-up in a subset of participants who completed both assessments

Behavioral analysis of the Probabilistic Gambling Task

For the pre-surgical evaluation (first evaluation), a two-sample t-test was conducted to compare the mean betting behavior on the risky option (25) between the mTLE-UHS and the control group. This option was selected for analysis because it represents a distinctly risky choice within the probabilistic gambling task, allowing for the investigation of potential differences in risk-taking behavior in mTLE-UHS patients. Then, to investigate potential differences in risky choice behavior, after surgery (second evaluation) a repeated-measures ANOVA (rmANOVA) was conducted on the percentage of choices selecting the risky option (25) in the probabilistic gambling task. The rmANOVA included Evaluation (Level 1: First, Level 2: Second) as a within-subjects factor and Group (Level 1: Control, Level 2: mTLE-UHS) as a between-subjects factor. This analysis allowed for the examination of potential differences in risky choice behavior

between the two groups across the two testing evaluations. Further independent two-sample t-test analysis was performed as post-hoc in order to compare the mean difference in risky choices between the two evaluations for each group. The analysis was performed using SPSS version 25.

fMRI Data Analysis

First-level analyses were based on a least-square estimation using a general linear model framework-following an event-related design including the experimental conditions of Gain (5+25+125) and Loss (5+25+125) as independent regressors in the design matrix, following convolution with the canonical hemodynamic response function. In the same way, onsets in which participants were presented with the fixation cross were included as a baseline. To account for movement-related noise, the six rigid-body motion parameters were included as nuisance regressors in the design matrix. The data was then high-pass filtered to a maximum of 1/128 Hz and correction for temporal autocorrelation using an autoregressive model of order 1. [AR(1)]. Non-sphericity correction was applied based on autocorrelation estimates, and global signal variance was normalized via proportional scaling.

The initial phase of analysis involved a whole-brain univariate approach to identify brain regions consistently activated during RP (gains and losses) within the probabilistic gambling task. Contrast images were generated to assess the effects of cumulative gains and losses relative to fixation specifically comparing [All Gain (5, 25, 125) vs. fixation] and [All Loss (5, 25, 125) vs. fixation]. Then, a one-sample t-test was conducted on the entire sample (i.e., Control and mTLE-UHS combined). Importantly, for the next sections these contrasts will be denominate as Gain and Loss conditions. Subsequent, one-way

ANOVAs were performed separately for Gains and for Losses to evaluate differences in activation between Controls and mTLE-UHS patients.

In the second phase, the effects of surgery in the reward-related system in mTLE-UHS patients were evaluated using rmANOVA. This model, similar to the behavioral rmANOVA model, tested the interaction between Group (Control vs. mTLE-UHS effect) and Evaluation (the effect of pre- and post- surgery). Specifically, we examined the effects of RP and Surgery in mTLE-UHS patients by independently contrasting the differential effects of Gains and Losses between evaluations (pre- and post-surgery) across the two groups.

Effects were considered statistically significant at the whole-brain level if they exceeded a voxel-wise threshold of $P < 0.005$ (cluster size $k > 20$ voxels extent) and cluster-level threshold of $P < 0.05$ (uncorrected). Peak activation coordinates within significant clusters were identified on the mean normalized T1-weighted structural image in MNI space and labeled according to the AAL (Automated Anatomical Labeling) atlas.

3. RESULTS

3.1. Behavioral findings (Probabilistic Gambling Task)

Overall, participants bet more times 25 than 5 (0.56 ± 0.24 % vs. 0.43 ± 0.24, t (47) =, $P < 0.053$). However, no significant differences were observed between mTLE-UHS patients and healthy controls, $t(46) = -1.087$, $p = 0.283$), suggesting similar average of risky choices distributions in both control and mTLE-UHS subjects. In addition, when we examined the effects of the surgery (second evaluation) in the mTLE-UHS patients, participants did not exhibited a change in their tendency to choose the riskier option (25

vs. 5) [$F(1, 42) = 0.252$, $p = .618$]. Similarly, no significant main effect of group was encountered [$F(1, 42) = 0.022$, $p = .882$]. Overall, no relevant differences were observed regarding decision making between both groups.

3.2. fMRI findings

Neural correlates of Gain and Loss processing

As expected, considering previous studies using the same gambling task (Camara et al., 2008, 2009, 2010a, 2010b), the analysis of functional MRI data during this monetary gambling task revealed overlapping patterns of neural activation associated with RP in both healthy controls and mTLE-UHS patients. Significant activations were observed during both gain and loss conditions in fronto-subcortical-limbic-parietal networks. This included bilateral activation in the ventral striatum/NAcc, extending to the caudate, amygdala, insular and parahippocampal cortex. Additionally, activations were observed in the prefrontal cortex (including the anterior cingulate cortex, the inferior and middle and dorsolateral prefrontal cortex), the inferior parietal cortex, and the middle occipital. Detailed information regarding the location and extent of activation clusters for both gain and loss conditions is presented in Figure 4 and Tables 2 and 3.

Gain and Loss Processing in mTLE-UHS patients

During gain processing, patients with mTLE-UHS compared to healthy controls exhibited reduced activity in the Unaffected Hemisphere (UH) amygdala-insula-superior temporal gyrus (STG) cluster (peak activity, MNI coordinates, x = 30, y = 4, z = -16, T =4.70, $P <$ 0.004; P-value at cluster level uncorrected). Additionally, during loss processing, we also observed reduced activity in the UH dorsolateral prefrontal cortex (DLPFC) (x = 44, y = 18, z = 38, T =4.14, $P <$ 0.008; (P-Value < 0.05 at cluster level) and the Affected

Hemisphere (AH) superior frontal gyrus (SFG), UH DLPFC (x = 44, y = 18, z = 38, *T* =4.14, *P* < 0.008; AH SFG, x = 0, y = 28, z = 50, *T* =3.94, for a p=0.048, *P* < 0.008; P-Value < 0.05 at cluster level). These findings are depicted in Figure 5A for the Gain condition and in Figure 5B for loss condition (see also Tables 4 and 5). Likewise, Figure 6 shows the parametric estimates (beta values analysis) of these differences of brain activation between groups and conditions, highlighting the differences in neural reward-related circuitry activation in mTLE-UHS patients.

Gain and Loss Processing in mTLE-UHS patients after surgery

The whole-brain voxel-wise ANOVA identified different regions with significant group by evaluation interaction. Specifically, for the Gain condition, we observed an interaction effect in some Regions of Interest (ROIs) -clusters- constituted by the AH SFG (x = -6, y = 32, z = 48, *T* =4.44, *P* < 0.022; P-Value < 0.05 at cluster level); AH inferior frontal gyrus (IFG) (x = -50, y = 14, z = 0, *T* =4.32, *P* < 0.011; P-Value < 0.05 at cluster level), AH STG (x = -48, y = 12, z = -12, *T* =3.73, *P* < 0.011; P-Value < 0.05 at cluster level), AH insula (x = -38, y = 16, z = -8, *T* =2.92, *P* < 0.011; P-Value < 0.05 at cluster level); and ventral striatum/NAcc (x = -8, y = 16, z = -2, *T* =4.05, *P* < 0.038; P-Value < 0.05 at cluster level) and pallidum (x = -10, y = 4, z = -2, *T* =3.47, *P* < 0.038; P-Value < 0.05 at cluster level). Additionally, interaction effects were observed in the UH, encompassing the middle temporal gyrus (x = 52, y = -20, z = -8, *T* =3.80, *P* < 0.025; P-Value < 0.05 at cluster level), insula (x = 46, y = -4, z = -6, *T* =3.55, *P* < 0.025; P-Value < 0.05 at cluster level) and the IFG (x = 44, y = 28, z = 16, *T* =3.61, *P* < 0.028; P-Value < 0.05 at cluster level).

Similarly, during the Loss condition, a positive interaction effect was observed in the AH, in clusters which include the SFG (x = -6, y = 32, z = 48, T =4.34, P < 0.022; P-Value < 0.05 at cluster level), the IFG (x = -50, y = 14, z = 0, T =4.25, P < 0.016; P-Value < 0.05 at cluster level), the STG (x = -48, y = 14, z = -12, T =3.50, P < 0.016; P-Value < 0.05 at cluster level), and the insula (x = -38, y = 16, z = -8, T =2.92, P < 0.016; P-Value < 0.05 at cluster level), the ventral striatum/NAcc (x = -8, y = 16, z = -2, T =3.94, P < 0.047; P-Value < 0.05 at cluster level) and the pallidum (x = -10, y = 4 , z = -4, T =3.41, P < 0.047; P-Value < 0.05 at cluster level). A significant interaction was also found in the UH IFG (x = 40, y = 38, z = 6, T =3.52, P < 0.040; P-Value < 0.05 at cluster level). These findings are showcased in Figure 7 and displayed upon in Tables 6 and 7.

To further investigate the observed effects, post-hoc analyses were performed using the parametric estimates difference between sessions (second evaluation vs first evaluation) in the three largest clusters, which included the structures of interest such us the AH (SFG), the insula, and the NAcc. The analyses focused on examining the direction of effects between groups (mTLE-UHS vs. healthy controls) and conditions (Gain vs. Loss) within these significant regions. Results indicated that the mTLE-UHS group exhibited statistically significant higher neural activation compared to the control group in the AH SFG Gain (Control: 0.19 ± 1.46 vs. mTLE-UHS: 1.05 ± 1.00, t (42) -2.31 = , P < 0.025), AH SFG Loss (Control: 0.24 ± 1.41 vs. mTLE-UHS: 1.03 ± 0.93, t (42) -2.20 =, P < 0.032); The IFG, STG, and insula Gain (Control: 0.61 ± 1.71 vs. mTLE-UHS: 1.97 ± 1.77, t (42) -2.57 =, P < 0.013), The IFG, STG, and insula Loss (Control: 0.59 ± 1.84 vs. mTLE-UHS: 1.97 ± 1.79, t (42) -2.52 =, P < 0.015); ventral striatum/NAcc and pallidum Gain (Control: 0.14 ± 1.42 vs. mTLE-UHS: 1.44 ± 1.28, t (42) -3.18 =, P < 0.002), ventral striatum/NAcc and pallidum Loss (Control: -0.03 ± 1.37 vs. mTLE-UHS: 1.31 ± 1.31, t

(42) -3.32 =, $P < 0.001$). Notably, this pattern did not exhibit a statistically significant difference between gain and loss conditions (see Figure 8 A, B, and C).

4. DISCUSSION

This study investigated the brain vulnerability of the RP in patients with mTLE-UHS during a probabilistic gambling task (monetary), compared with healthy controls. Additionally, we studied the impact of epilepsy surgery on this system. Pre-surgical analysis (first evaluation) revealed significant differences in brain activity between mTLE-UHS and healthy controls during both gain and loss processing. Specifically, patients with mTLE-UHS exhibited reduced activity in the UH amygdala-insula-STG and UH-DLPFC during gain and loss processing. Additionally, a reduced activity in the AH SFG was found during loss processing. Post-surgical analysis, second evaluation, demonstrated significant group by evaluation interaction, with similar effects in both conditions. More precisely, these effects were found in the AH SFG, IFG, STG, insula, ventral striatum/NAcc and pallidum in the AH, while in the UH it was only evident in the IFG. By the other hand, for gain condition the effect was also found in the UH insula. Importantly, post-hoc analyses of these interaction effects using the differences of parametric estimates between evaluations revealed statistically significant higher BOLD respond activity in the mTLE-UHS group compared to the healthy control group within these brain regions, predominantly in the AH. Notably, this difference was not significant between gain and loss conditions, suggesting a general increase in neural activity within these reward-related structures regardless of the valence of the outcome. Interestingly, at behavioral level we did not find statistically significant differences between groups and sessions in the probabilistic gambling task. These findings warrant further investigation

into the long-term impact of mTLE-UHS on decision-making and potential interventions to address these challenges.

4.1. Reward-related network initial disfunction in mTLE-UHS

The participants in this study exhibit unilateral hippocampal sclerosis, a defining characteristic of their condition, but it is not present in all patients with mTLE. Previous neuroimaging investigations demonstrated that this structural lesion, along with the associated epileptogenic activity, is known to induce changes in brain structures and neural circuits related with the mesial temporal lobe (de Campos et al., 2016; Maller et al., 2019; Roger et al., 2020; Morgan et al., 2021), including those involved in RP and decision-making (Martínez-Selva et al., 2006). This study provides relevant information about the brain structures potentially affected by mTLE-UHS.

As was exposed previously, mesial temporal lobe structures such as the hippocampus and amygdala are related with the RP network (Murray, 2007; Liu et al., 2011; Perlman et al., 2012; Sadler et al., 2020; Manssuer et al., 2022). The affectation of these regions have importantly impact boarder brain networks (Li et al., 2017, 2021c; Lee et al., 2018). To understand the implications of these findings, we will discuss the specific brain regions that show reduced activity in this study, the feedback valence (gain or loss) associated with these differences, and the hemispheric localization of these regions relative to the lesion (AH or UH).

Brain regions with reduced activity and their implications in reward processing

Our analysis identified several key regions exhibiting reduced activity in mTLE-UHS patients: the amygdala, insula, STG, DLPFC, and SFG. These structures are implicated

in various aspects related to RP and decision-making. For example, the amygdala is a crucial brain region for emotional processing (Bigot et al., 2020; Inman et al., 2020), particularly fear and anxiety (Sun et al., 2020; Zundel et al., 2022; LeDuke et al., 2023), but also plays a role in associating rewards with specific stimuli and contexts. More specifically, studies have shown its involvement in emotional tagging, reward-related learning, and risk aversion (Schultz et al., 1997; Pessoa and Adolphs, 2010; LeDoux, 2012). The attenuated response in the amygdala could reflect a disrupted RP pathway in mTLE-UHS patients, aligning with existing research that points to a compromised limbic function within this population (Pizzanelli et al., 2022). Also, the insula, often referred to as the "interoceptive cortex," integrates sensory, emotional, and cognitive information to create subjective feelings. It has been implicated in functions such as gut feeling and reward valence, risk assessment and interoception, and integrating rewards with context (Paulus and Stein, 2006; Craig, 2009). By the other hand the STG is involved in a wide range of cognitive functions, including social perception, auditory processing, and language comprehension, which are crucial for understanding reward-related information presented verbally and in social contexts (Rauschecker and Tian, 2000; Frith and Frith, 2010). The DLPFC is related to executive control, playing a critical role in goal-directed behavior, inhibitory control, and working memory, all of which are essential for making informed decisions (Miller and Cohen, 2001; Diamond, 2013). The DLPFC's role in cognitive control (Aouizerate et al., 2004) and executive function (Alameda et al., 2022), underscores a broader impact on cognitive operations beyond reward valuation. Finally, the SFG is involved in a broader range of reward-related processes, including value-based decision-making, goal-directed behavior, cognitive control, working memory, and feedback processing (Fuster, 2001; Miller and Cohen, 2001; Holroyd and Coles, 2002; Hare et al., 2009; Baddeley, 2012). Overall, these findings suggest that mTLE-UHS

patients could exhibit challenges in integrating diverse positive and negative stimuli and processing them at varying levels, encompassing both cognitive and affective dimensions. This might denote a broader impairment in the ability to learn from both rewarding and punishing experiences, potentially impacting adaptive behavior and decision-making. This pattern aligns with previous studies that have shown altered neural circuitry and connectivity in the reward system in mTLE patients (Cataldi et al., 2013; Tong et al., 2019; Ma et al., 2023), potentially contributing to cognitive and emotional disturbances, including anhedonia and impaired decision-making (Lothe et al., 2008; Bonatti et al., 2009; Labudda et al., 2009; Delazer et al., 2010; Hennion et al., 2015; Zhang et al., 2018; Simsekoglu et al., 2022; Vilà-Balló et al., 2022).

2. Clinical Relevance of feedback valence and decreased neural BOLD response

Our findings highlight a potential disruption in the processing of both positive and negative feedback in mTLE-UHS patients, evident in the reduced activity observed in the amygdala, insula, STG, and DLPFC during both gain and loss processing (Vilà-Balló et al., 2022). This could potentially translate to a diminished ability to learn from both rewarding and punishing experiences, affecting adaptive behavior and decision-making (Casey et al., 2019).

The reduced activity in the amygdala, a key region for emotional processing and reward-related learning (Schultz et al., 1997; Pessoa and Adolphs, 2010; LeDoux, 2012), during both gain and loss processing, could indicate a diminished capacity to assign emotional significance to both positive and negative experiences. This might translate to a reduced ability to learn from both rewarding and punishing outcomes, potentially contributing to maladaptive behavior and a reduced capacity to experience pleasure (anhedonia)

(Delgado, 2007; Der-Avakian and Markou, 2012). Similarly, reduced activity in the insula, crucial for integrating sensory, emotional, and cognitive information, particularly interoceptive signals related to reward and risk (Paulus and Stein, 2006; Craig, 2009), during both gain and loss, suggests a potential impairment in the ability to accurately perceive and interpret internal bodily states associated with both positive and negative feedback. This could affect the subjective experience of reward and punishment, potentially leading to difficulties in adjusting behavior based on these feelings and contributing to anhedonia (Keller et al., 2013; Rzepa and McCabe, 2019). The reduced activity in the STG, involved in social perception, auditory processing, and language comprehension (Rauschecker and Tian, 2000; Friederici, 2011), during both gain and loss, suggests a potential impairment in interpreting reward-related information presented verbally and in social contexts. This could contribute to social withdrawal and emotional difficulties, further contributing to anhedonic symptoms (Yang et al., 2017; Xia et al., 2019; Zacková et al., 2021).

The DLPFC, critical for cognitive control, working memory, and inhibiting impulsive behavior, also showed reduced activity during both gain and loss processing, potentially indicating a broader impairment in executive function. This could lead to difficulties in making informed decisions, potentially contributing to impulsivity and difficulty regulating mood, often seen in depression (Han et al., 2023). Interestingly, the SFG demonstrated reduced activity solely during loss processing, probably in relation with a specific deficit in integrating negative feedback and potentially impacting the ability to adjust behavior based on negative experiences (Der-Avakian and Markou, 2012; Hanganu-Opatz et al., 2023). This suggests that mTLE-UHS could be associated with a

heightened sensitivity to negative experiences, potentially contributing to difficulties in regulating mood and motivation, often observed in depression (Preglej et al., 2021).

These findings highlight the potential for mTLE-UHS to disrupt various components of the reward system, potentially leading to challenges in learning from both positive and negative feedback. This, in turn, could impact an individual's ability to experience pleasure, regulate their mood, and make informed decisions, aligning with the prevalence of anhedonia and other mood-related challenges in this population. The specific involvement of the SFG in processing negative feedback suggests that mTLE-UHS might not only disrupt the general ability to learn from experience but also have a specific impact on how individuals respond to negative outcomes, potentially contributing to the heightened sensitivity to negative experiences observed in depression.

3. Hemispheric localization of reduced activity and contralateral effects

Our analysis revealed that a larger number of areas exhibiting reduced activity were located in the hemisphere contralateral to the lesion, highlighting that the impact of the epileptogenic focus extends to the opposite hemisphere, UH, compared to the AH. this result indicates that the impact extends beyond a focal effect and involves network-based alterations (Li et al., 2021a; Y et al., 2024). These network-based alterations refer to disruptions in the functional and structural connectivity within the brain's neural networks, including changes in synaptic connections and neural pathways that facilitate communication between different brain regions. In the context of epilepsy, this could mean altered synchronization between the hemispheres, disruptions in the default mode network (DMN), and changes in the connectivity of the hippocampus with other brain regions (Cataldi et al., 2013; Lee et al., 2021; Li et al., 2021a). These disruptions can lead

to a cascade of effects impacting cognitive functions, emotional regulation, and overall brain network efficiency, further complicating the clinical presentation and management of epilepsy. By the other hand, our findings could be also attributed to the phenomenon, termed "contralateral effects," has been documented in different contexts such as the Rasmussen encephalitis (Cay-Martinez et al., 2020), suggesting a complex interplay between the two hemispheres in response to the epileptogenic focus. Additionally, genetic investigations profiling neuronal and glial populations in comparative animal models revealed pronounced detrimental effects in contralateral brain structures (Berger et al., 2020). This is further corroborated by metabolic analysis in patients with mTLE, which showed bilateral cerebral involvement, with the contralateral impact becoming more apparent when using hippocampal-specific techniques, potentially indicating a diminution of interhemispheric connectivity (Wang et al., 2019). This bilateral asymmetry in structural abnormalities correlates with the findings of Whelan and colleagues, who identified both ipsilateral and contralateral alterations across common epileptic disorders, with a pronounced disparity in contralateral impairments between right and left mTLE, with a heightened severity observed in right hemisphere lesions (Whelan et al., 2018). This lesion-dependent variance has been consistently documented in pre- and post-surgical contexts of epilepsy intervention (Elkommos et al., 2015; Morgan et al., 2019).

Our findings resonate with current scientific evidence, indicating that mTLE-UHS may entail widespread neural consequences (Whelan et al., 2018; Lopez et al., 2022), potentially influencing a variety of cognitive domains, including the those related with RP (Krámská et al., 2018). The decreased activation in these areas during reward-related tasks suggests a neurological basis for the cognitive and emotional challenges observed

in individuals with mTLE-UHS. This adds to the growing body of evidence that emphasizes the need for comprehensive approaches to epilepsy treatment, which address not only the seizures but also the broader neuropsychological impairments and mood symptomatology associated with the disorder. These results underscore the condition's pervasive impact on brain function and highlight the necessity for further research into tailored therapeutic interventions. These should aim not only to mitigate seizure activity but also to support cognitive and emotional health, potentially enhancing quality of life for individuals with epilepsy.

4.2. Postsurgical effects on the reward-related network

While pre-surgical analysis revealed reduced activity in key brain regions involved in processing both gains and losses, post-surgical analysis revealed a significant interaction effect between group and evaluation, highlighting changes in the neural activity of the mTLE-UHS cohort. Specifically, the increased BOLD response, primarily observed in the AH in both conditions. This shift in activation patterns is particularly notable within AH, where pre-surgically, a reduction in activity was observed in the AH during both gain and loss processing. However, post-surgery, a statistically significant increase in activity was found in the AH, including the SFG, IFG, STG, insula, ventral striatum/NAcc, and pallidum. This suggests that these regions, crucial for various aspects of RP and decision-making (Fauth-Bühler et al., 2014; Reckless et al., 2014; Yang et al., 2016; Zhang et al., 2019; Loued-Khenissi et al., 2020; Radoman et al., 2021; Fujiyama et al., 2022; Kim et al., 2023; Liu et al., 2023a, 2023b), exhibit a different pattern of activity post-surgery in mTLE-UHS patients. This finding, while seemingly counterintuitive given the surgical resection, aligns with a growing body of research demonstrating that brain structural and connectivity investigations have shown significant changes in brain

function following epilepsy surgery (Li et al., 2021c, 2021b, 2022). For example, Li et al. (2022) examined changes in brain connectivity following temporal lobe epilepsy surgery using diffusion tensor imaging and found a significant decrease in white matter integrity in the affected hemisphere. This suggests that surgical resection can lead to structural changes in the brain that impact neural communication. While their study focuses on white matter changes, it suggests that the brain undergoes a significant reorganization process after surgery. This reorganization might involve the recruitment of alternative pathways, leading to increased activity in the affected hemisphere, as a way to compensate for the loss of function. Moreover, Li et al. (2021a) conducted a comprehensive review of neural plasticity and functional reorganization following epilepsy surgery. Their findings highlight the complex interplay between the surgical intervention and the ongoing disease process, emphasizing the importance of understanding these changes for optimizing patient outcomes. Their review underscores the potential for the brain to adapt to the effects of surgery, which may manifest as changes in neural activation patterns. Li et al. (2021b) examined the impact of epilepsy surgery on cognitive function and found that while surgery can improve seizure control, it may also have long-term consequences for cognitive abilities. Their findings emphasize the need for comprehensive assessments and targeted interventions to address these potential cognitive deficits. This aligns with our findings, as the increased activity in the affected hemisphere might reflect a complex interplay of compensatory and adaptive mechanisms in response to the disease process and the surgical intervention. This increased activity in the AH, particularly in the SFG, insula, and NAcc, might reflect a post-surgical recalibration of neural networks, potentially representing a compensatory mechanism or a reorganization of functional networks. Further analysis revealed that this increased activity was not specific to gain or loss conditions, indicating a general shift in

neural activity within these structures, potentially reflecting a broader adaptation to the effects of the disease and/or surgical intervention. Further analysis revealed that this increased activity was not specific to gain or loss conditions, indicating a general shift in neural activity within these structures.

Also, this heightened activation could reflect several factors, including: **(i)** Compensatory mechanisms (Bettus et al., 2009; Zhao et al., 2018; Vega-García et al., 2022); **(ii)** neuroplastic reorganization, similarly to the effects observed in stroke, brain injury and other kind of brain surgeries such as hemispherectomy (Lim and Salvatore, 2014; Gaubatz et al., 2020; García-Casares et al., 2022); and **(iii)** disease-related neuroplasticity (Bourdillon et al., 2017; Jarero-Basulto et al., 2018; Serrano-Castro et al., 2020). For example, the increased activity in the AH might represent the brain's attempt to compensate for the disrupted circuitry following resection, or it could reflect the reorganization of neural pathways in response to both the disease and the surgical intervention (Li et al., 2021c). However, the involvement of the UH IFG during both gain and loss conditions suggests a potential compensatory role of the contralateral hemisphere in managing the altered reward-related circuitry (Bettus et al., 2009).

Understanding the mechanisms driving these post-surgical changes in brain activity is crucial for optimizing long-term outcomes for patients with mTLE-UHS. Further investigation is needed to determine whether this heightened activity represents a beneficial compensatory response or a maladaptive consequence of the disease and/or surgery. The potential for targeted interventions aimed at enhancing these compensatory mechanisms or mitigating any adverse effects is an area warranting further investigation which may include the study of individual differences and brain connectivity.

Behavioral findings interpretation

The lack of statistically significant differences between groups and in the probabilistic gambling task, both in the first and second evaluations, is consistent with findings from other studies suggesting that mTLE-UHS does not demonstrably impact decision-making under conditions of risk (Bonatti et al., 2009; Labudda et al., 2009; Delazer et al., 2010; Vilà-Balló et al., 2022)). This lack of a significant difference could be attributed to a lack of sensitivity of the task, potentially failing to detect subtle changes in risk-taking behavior, as evidenced by previous electrophysiological studies (Vilà-Balló et al., 2022).

Limitations

Within the purview of our study's contributions to the understanding of pre- and post-surgical neural dynamics in mTLE-UHS, we must acknowledge certain constraints that temper our conclusions. Firstly, the absence of clinical data regarding affective states, such as depression and anhedonia, both before and after surgery, limits our ability to explore the potential relationship between alterations in reward-related neural activity and these clinically significant symptoms. Future research should consider incorporating a more detailed assessment of affective states to gain a more holistic understanding of the patient's psychological well-being. It is important to note that the relatively small sample size of this study could impact the generalizability of our findings and the statistical power to detect more subtle behavioral disturbances. Future studies with larger cohorts are essential to validate and extend our observations.

Future studies

Future research should address these limitations to strengthen the validity of the findings and gain a more comprehensive understanding of mTLE-UHS. Specifically:

Larger sample size: Replicating the current study with a larger sample size would enhance the generalizability of the findings specially at behavioral level.

Multimodal profiles and individual differences: Including multimodal assessments of mTLE-UHS, incorporating clinical, neuropsychological, and neuroimaging data, would provide a more detailed understanding of individual differences in disease progression and the impact of surgery. This could also guide personalized surgical strategies.

Connectivity analyses: Investigating network-level changes in reward processing using connectivity analyses, both pre- and post-surgery, could offer a more holistic understanding of neuroplasticity associated with mTLE-UHS (Camara et al., 2009).

Comprehensive affective assessment: Integrating a comprehensive clinical assessment of affective states, both pre- and post-surgery, would allow for a more complete understanding of the impact of mTLE-UHS and surgical intervention on patients' psychological well-being.

Exploration of the reward system beyond valuation: Utilizing tasks that engage other aspects of the reward system beyond valuation could provide a more comprehensive picture of reward processing in mTLE-UHS patients.

Interplay with Decision-Making: Further research should investigate the interplay between observed neural changes and decision-making processes in mTLE-UHS patients, exploring the functional implications of these alterations.

CONCLUSION

This study aimed to investigate the neural correlates RP in patients with mTLE-UHS, comparing them to healthy controls before and after epilepsy surgery using fMRI techniques and a PGT. Our findings confirmed that mTLE-UHS is associated with altered brain reward activation patterns, both before and after epilepsy surgery. Pre-surgical analysis revealed reduced activity in key brain regions involved in processing both gains and losses, suggesting impaired processing of both positive and negative feedback, highlighting the broader impact of the epileptogenic focus on brain networks beyond the immediate site of the lesion. This was particularly evident in the UH amygdala-insula-STG and UH-DLPFC. Additionally, reduced activity in the AH superior frontal gyrus (SFG) was found during loss processing.

Post-surgical analysis revealed a significant group by evaluation interaction effect, suggesting a distinct pattern of neural activity in mTLE-UHS patients after surgery, particularly within the AH. This heightened activity in the AH, observed in the SFG, IFG, STG, insula, ventral striatum/NAcc, and pallidum, suggests a complex interplay between the disease process and surgical intervention. This increase in activation might reflect compensatory mechanisms, neuroplastic reorganization, or pre-existing disease-related neuroplasticity.

While the behavioral data did not reveal significant differences in risk-taking behavior between groups, the observed neural alterations highlight the potential disruption of RP networks in mTLE-UHS. These findings emphasize the need to further investigate the long-term impact of these changes on cognitive function, emotional regulation, and overall well-being in patients with mTLE-UHS. Understanding the mechanisms driving

these changes and exploring potential interventions to optimize long-term outcomes for these patients remains a crucial area of future research.

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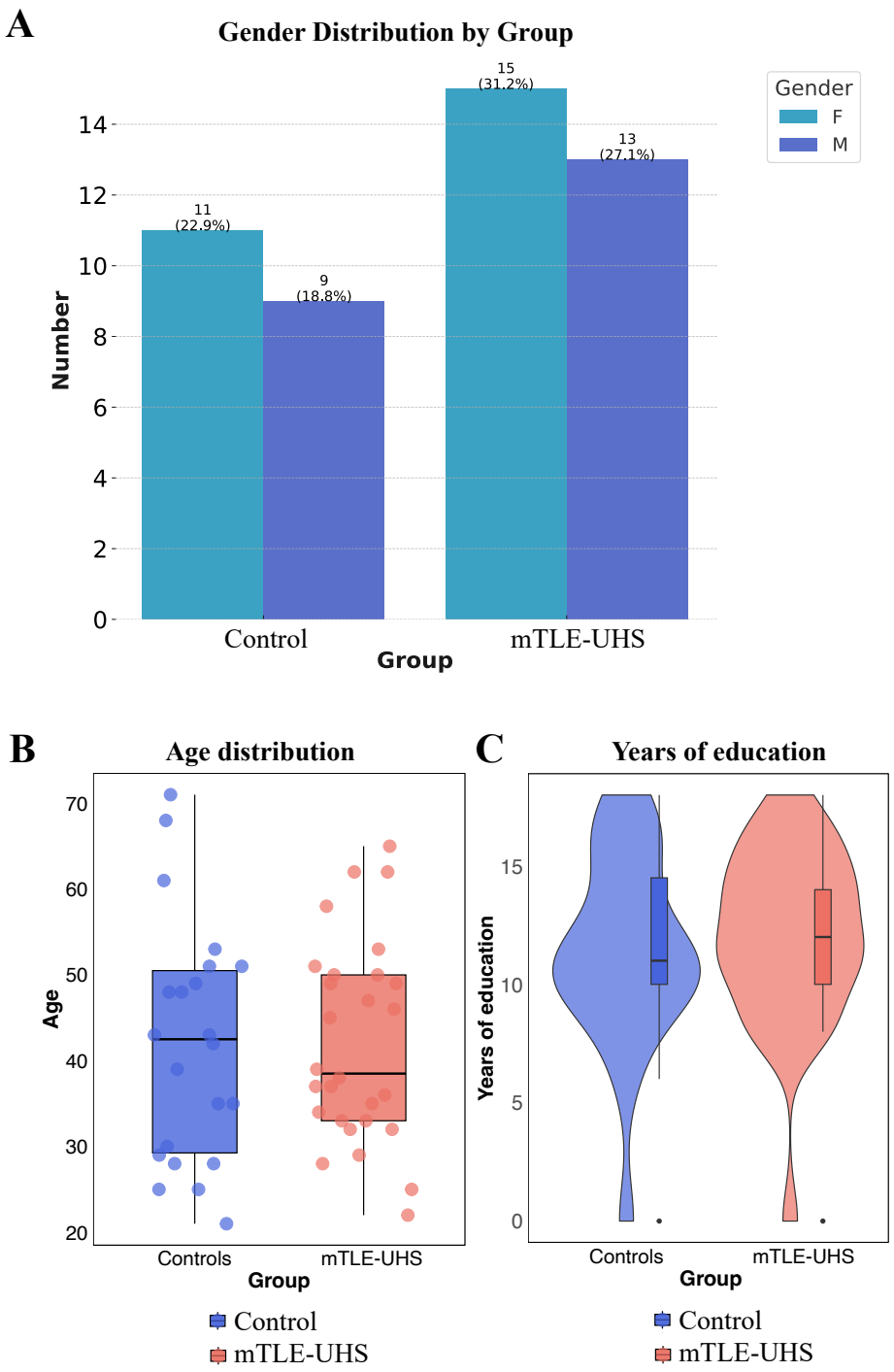


Figure 1: Demographic characteristics of mTLE-UHS and controls.
A. illustrates the gender distribution across the study groups, showcasing the number of male (M) and female (F) participants, differentiated by color and display the count and corresponding percentage of participants relative to the total sample size. **B.** Depicts the age distribution within the patient and control groups. Box plots convey the median, quartiles, and range, offering a visual summary of the central tendency and dispersion of ages across both cohorts. **C.** Illustrates the years of education for the study participants, categorized by patient and control groups. The Butterfly plot highlight the median, interquartile range, and outliers, facilitating a comparison of educational background between the cohorts.

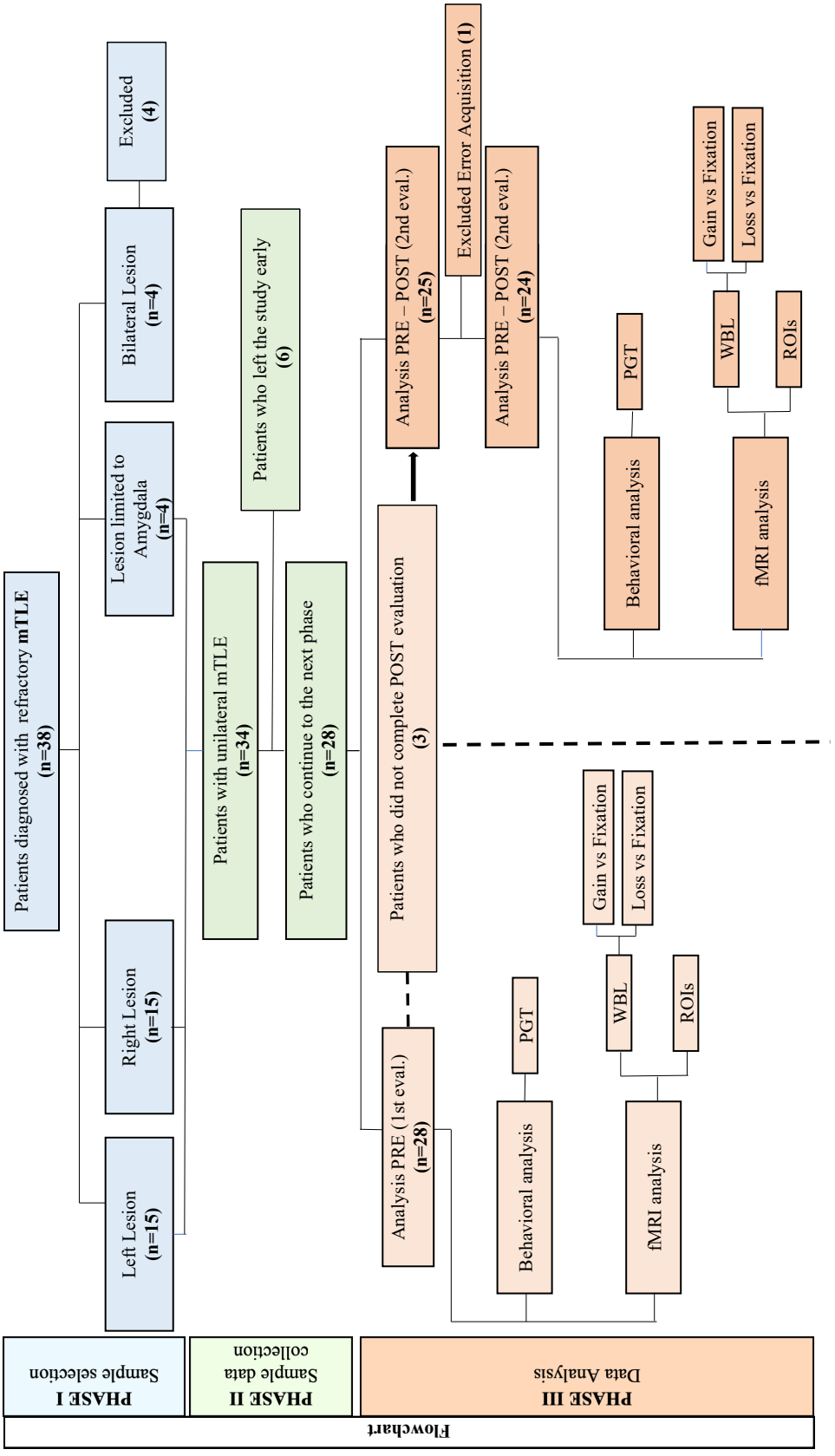


Figure 2: Flowchart for patients' selection in the study.
The following abbreviations were employed: mTLE (Mesial Temporal Lobe Epilepsy), mTLE-UHS (Mesial Temporal Lobe Epilepsy with Unilateral Hippocampal Sclerosis), PGT (Probabilistic Gambling Task), fMRI (Functional Magnetic Resonance Imaging), WBL (Whole Brain Level), ROIs (Regions of Interest), PRE (Presurgical-evaluation phase, corresponding to first evaluation), and POST (Postsurgical-evaluation phase, corresponding to second evaluation).

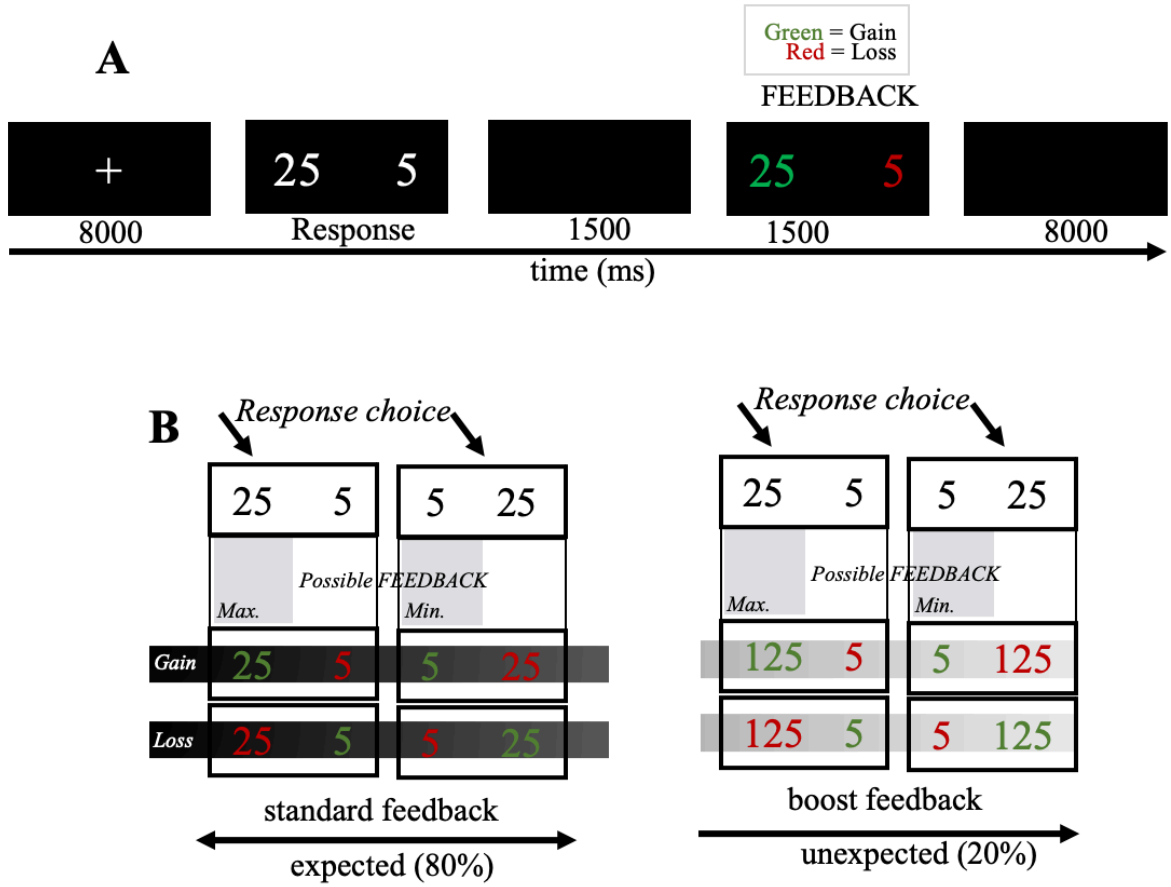


Figure 3: Design of a probabilistic gambling task for mTLE-UHS and controls.
(A) depicts the timeline of the probabilistic gambling task, beginning with a fixation cross, followed by a choice between two numerical options, and concluding with colored feedback indicating monetary gain or loss. **(B)** contrasts of standard and boost feedback scenarios.

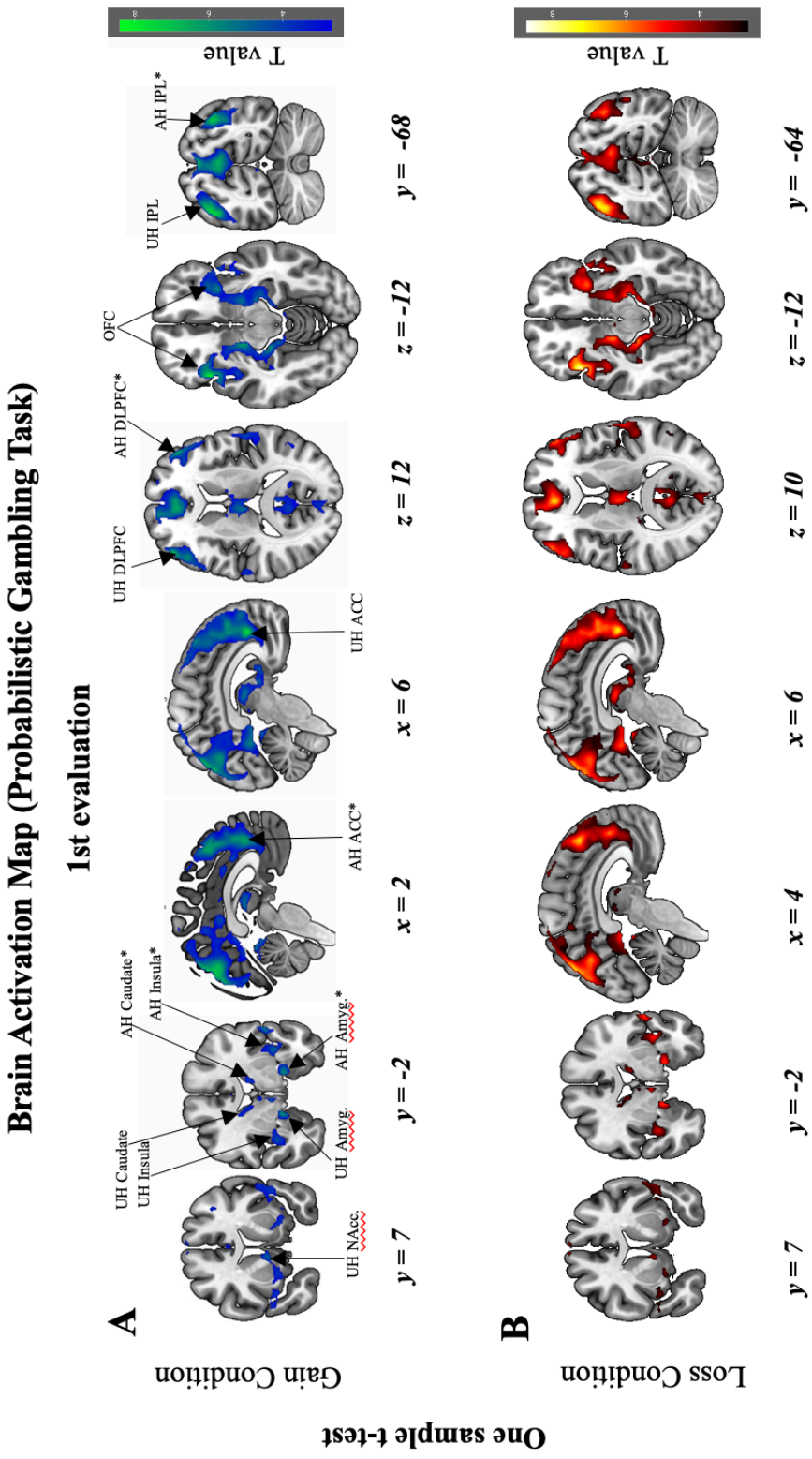


Figure 4: Univariate fMRI analysis in gain and loss condition.
Displayed are comprehensive coronal, sagittal, and axial brain scans demonstrating functional activity during a probabilistic gambling task, set against a structural MRI within a standardized stereotactic space, highlighted by T-score maps. The figure contrasts neural activity during the task's gain and loss conditions against a fixation baseline. (**A)** Gain Condition: Significant activation is observed in regions critical to reward processing, including the Unaffected hemisphere Nucleus Accumbens (UH NAcc.), Unaffected hemisphere Amygdala (UH Amyg.), Unaffected hemisphere Insula (UH Insula), Unaffected

hemisphere Caudate (UH Caudate), Unaffected hemisphere Anterior Cingulate Cortex (UH ACC), Unaffected hemisphere Dorsolateral Prefrontal Cortex (UH DLPFC), and Unaffected hemisphere Inferior Parietal Lobule (UH IPL). Notably, an asterisk (*) marks the corresponding regions in the Affected hemisphere, denoting the side affected by the epileptogenic lesion in this study: Affected hemisphere Caudate (AH Caudate), Affected hemisphere Insula (AH Insula), Affected hemisphere Amygdala (AH Amyg.), Affected hemisphere Anterior Cingulate Cortex (AH ACC), Affected hemisphere Dorsolateral Prefrontal Cortex (AH DLPFC), Affected hemisphere Inferior Parietal Lobule (AH IPL). **(B)** Loss Condition: Presents a pattern of activation across similar regions as the gain condition, albeit with differing T values, reflective of the brain's response to potential negative outcomes. The color-coded scales adjacent to each scan provide a quantifiable measure of activation intensity, with the brain slices positioned at precise MNI coordinates for clear anatomical identification. This visualization captures the dynamic cerebral responses to reward and risk, as influenced by the pathology of mTLE-UHS.

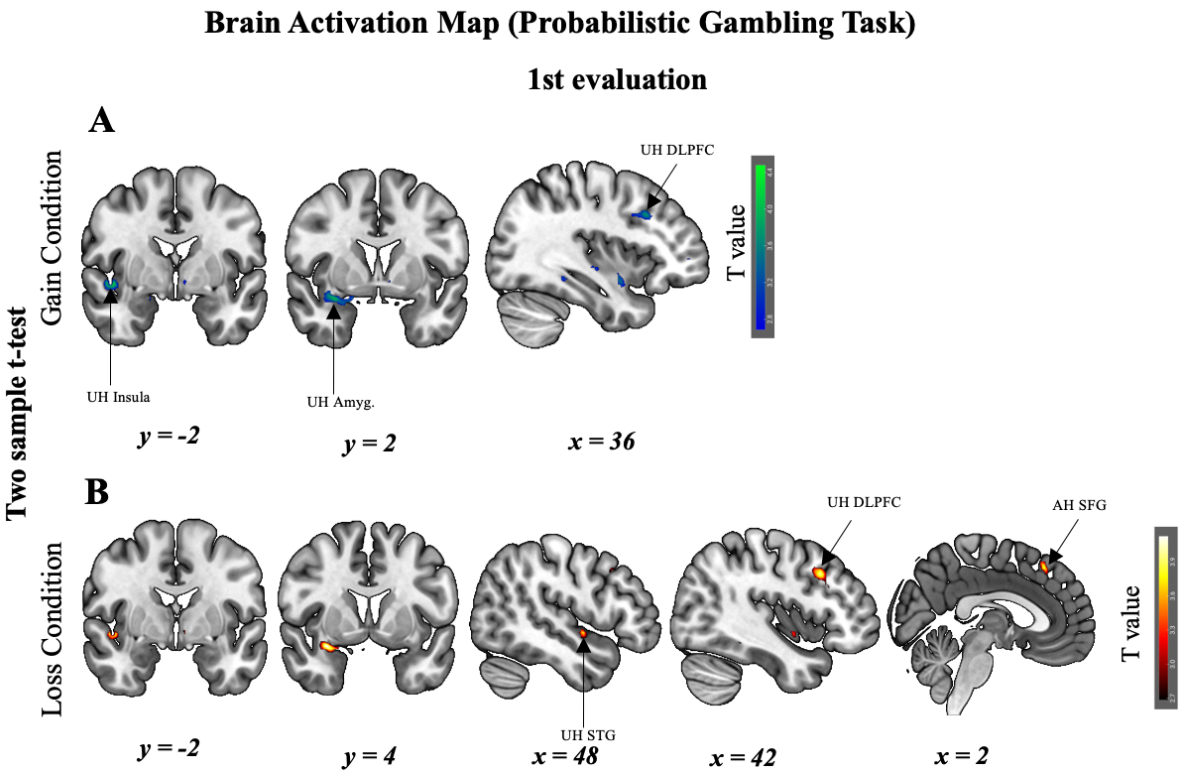


Figure 5. Region of Interest for gain and loss condition.
A depicts brain regions activated in the gain condition, highlighting the Unaffected hemisphere Insula (UH Insula), Unaffected hemisphere Amygdala (UH Amyg.), and Unaffected hemisphere Dorsolateral Prefrontal Cortex (UH DLPFC), indicative of their involvement in reward processing. **B** illustrates the loss condition, showing significant activity in the Unaffected hemisphere Temporal Superior Gyrus (UH TSG) and Affected hemisphere Frontal Supramarginal Gyrus (AH FSM), regions implicated in evaluating negative outcomes. Activation is overlaid on a standard brain template for visual reference. T values are represented by the color bar, denoting the statistical intensity of brain activity, with blue to green shades indicating increased activation within these regions**.**

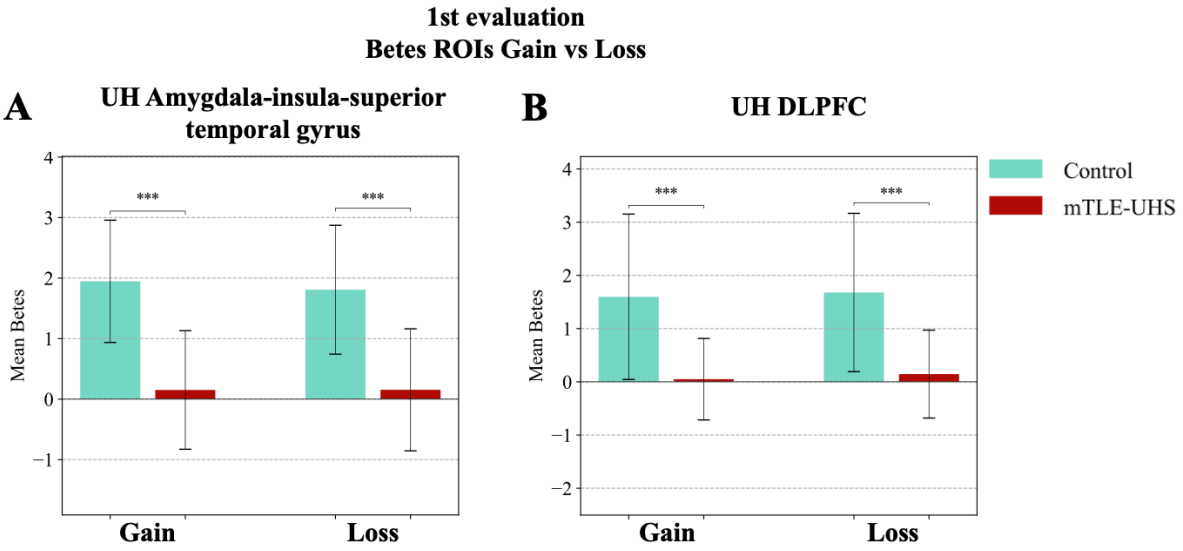


Figure 6: Differential Beta Value analysis between groups in gain and loss condition. Comparison of neural activation in mTLE-UHS patients against controls in response to monetary gains and losses, highlighting diminished patterns in the Unaffected hemisphere Amygdala-insula-superior temporal gyrus (UH Amygdala-insula-superior temporal gyrus) **(A);** and Unaffected hemisphere Dorsolateral Prefrontal Cortex (UH DLPFC) **(B).**

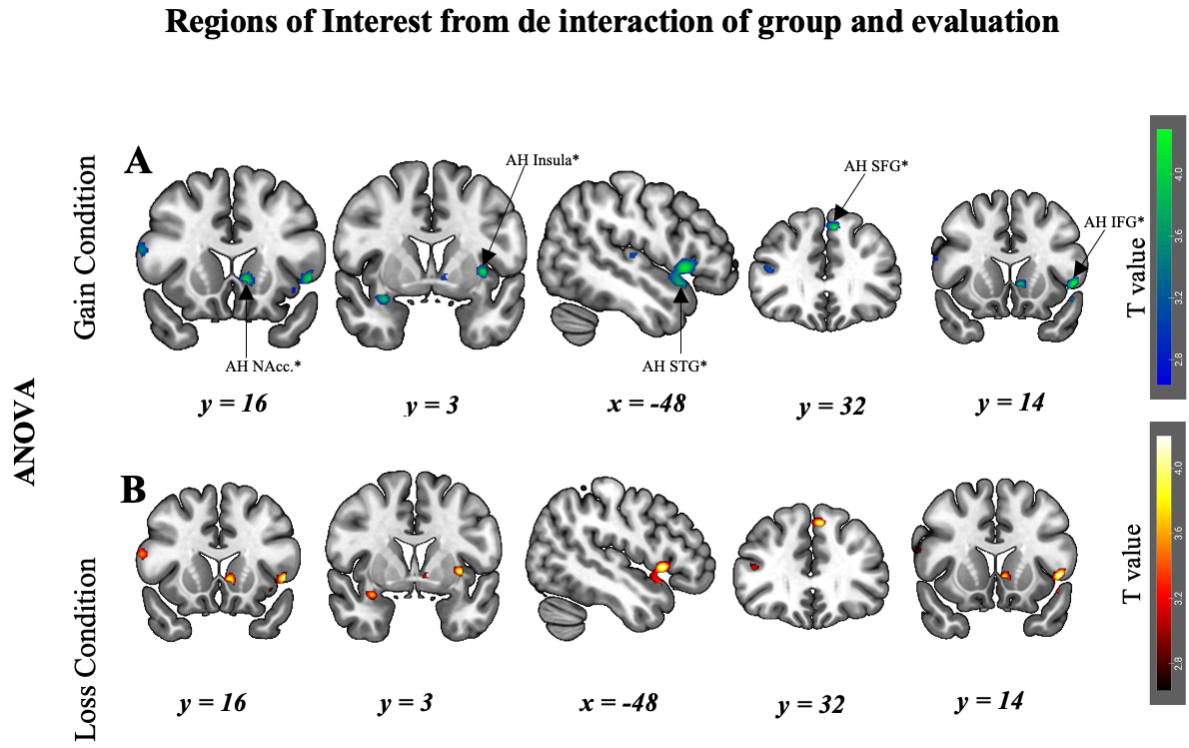


Figure 7: Brain activation changes in mTLE-UHS patients and controls through evaluations.
A (Gain Condition): The top row represents brain activation differences in the gain condition, comparing controls and mTLE-UHS patients before and after epilepsy surgery, showing notable changes in the Affected hemisphere nucleus accumbens (AH NAcc.), Affected hemisphere insula (AH Insula), and other significant regions. **B** (Loss Condition): The bottom row illustrates contrasting activation in the loss condition, with marked variations seen in the same group comparison, post-surgery.

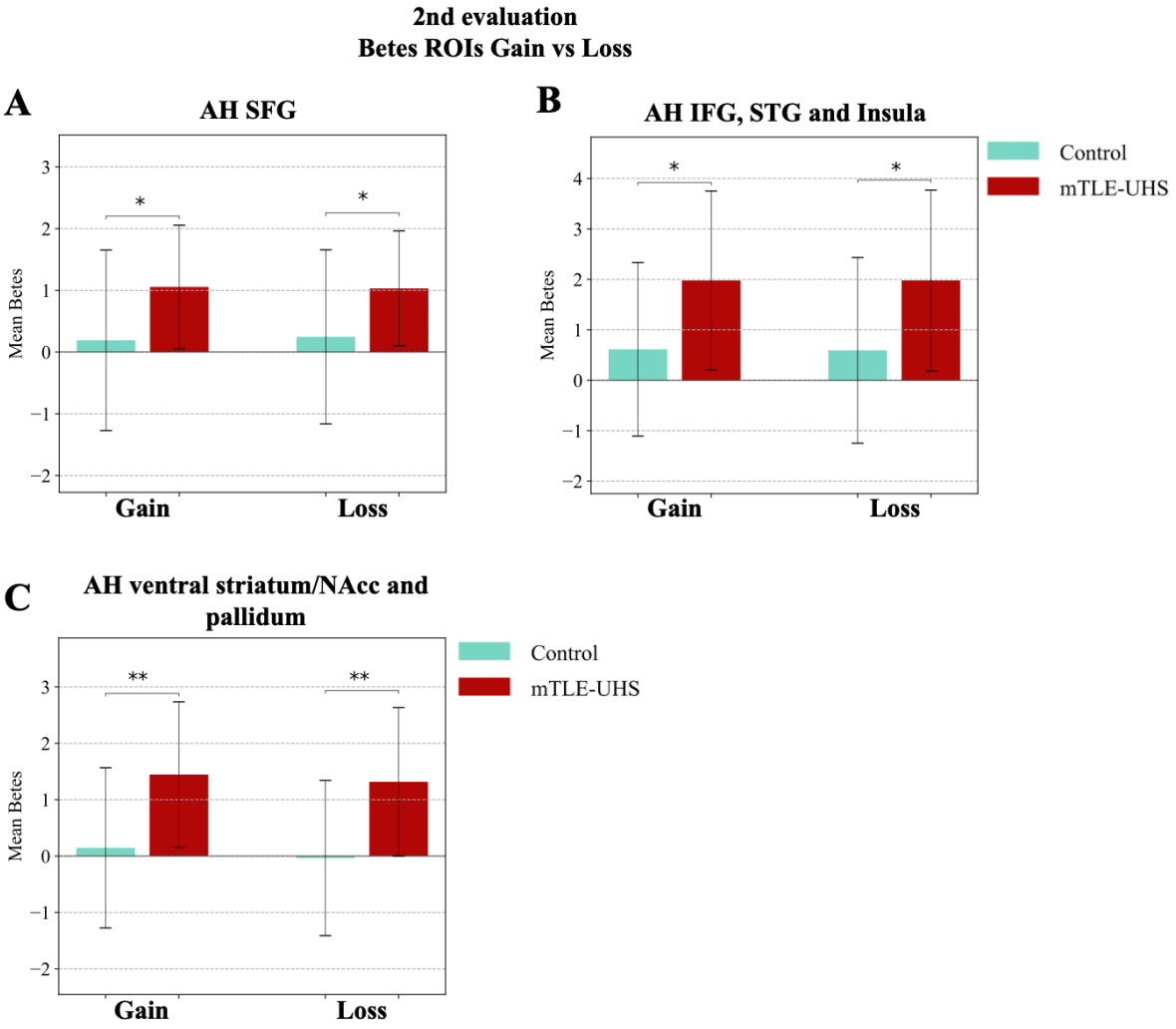


Figure 8: Differential beta value analysis between groups in gain and loss condition. Comparison of neural activation in mTLE-UHS patients against controls in response to monetary gains and losses, highlighting distinct patterns in the Affected hemisphere Superior Frontal Gyrus (AH SFG) **(A)**, Affected hemisphere inferior frontal gyrus (AH IFG), superior temporal gyrus (STG), and Insula **(B)**, and Affected hemisphere (AH) ventral striatum/NAcc and pallidum **(C)**.

Table 1: Participants' sociodemographic and clinical data

Code	Sex	Age	Edu	Lesion side	Onset dis	Duration	Freq	FIAS	FBTCS	AEDS	BZD, BARB & PB
ep01	M	45	16	TLE R	10M	45Y	1–2/mo	Yes	No	4	No
ep02	F	37	8	TLE L	14M	36Y	1–2/mo	Yes	Yes	3	Clobazam 10 mg/d
ep04	M	51	11	TLE R	11Y	40Y	1/mo	Yes	No	3	Clobazam 20mg/d
ep05	M	37	11	TLE R	18Y	19Y	4–6/mo	Yes	Yes	3	Phenobarbital 100 mg/d
ep06	F	28	8	TLE L	2Y	26Y	4-5/mo	Yes	Yes	2	No
ep07	F	35	10	TLE L	20Y	15Y	1-3/mo	Yes	Yes	3	Clobazam 15mg/d
ep08	F	50	8	TLE R	18Y	32Y	6–8/mo	Yes	Yes	3	Phenobarbital 100 mg/d
ep09	F	62	0	TLE L	4Y	58Y	4–5/mo	Yes	Yes	2	Phenobarbital 100 mg/d
ep10	M	65	8	TLE R	41Y	24Y	4/mo	Yes	No	2	No
ep11	F	33	11	TLE L	16Y	17Y	30–35/mo	Yes	Yes	3	Clobazam 10 mg/d
ep12	M	32	16	TLE R	23Y	9Y	8–10/mo	Yes	Yes	2	No
ep13	M	38	16	TLE L	32Y	6Y	2–4/mo	Yes	Yes	3	No
ep14	M	22	16	TLE R	17Y	5Y	5/mo	Yes	Yes	2	No
ep15	F	47	12	TLE L	13M	46Y	7–9/mo	Yes	No	2	No
ep18	F	39	14	TLE L	12M	38Y	5–6/mo	Yes	Yes	4	Phenobarbital 150 mg/d
ep19	F	34	14	TLE R	10Y	24Y	3/mo	Yes	No	2	No
ep21	M	62	12	TLE R	31Y	31Y	4–5/mo	Yes	Yes	3	No
ep22	M	29	14	TLE L	15Y	14Y	3–4/mo	Yes	Yes	3	Phenobarbital 200 mg/d
ep25	M	25	9	TLE L	13Y	12Y	1/mo	Yes	Yes	2	No
ep27	F	50	14	TLE L	32Y	18Y	9-10/mo	Yes	No	3	Clobazam 25mg/d
ep29	F	33	12	TLE R	21Y	12Y	2/mo	Yes	Yes	2	No
ep30	M	49	11	TLE R	2Y	47Y	2/mo	Yes	Yes	3	Clonazepam 1mg/d
ep33	M	49	10	TLE R	1Y	48Y	4-5/mo	Yes	No	2	No
ep34	F	46	14	TLE L	8Y	38Y	18–20/mo	Yes	Yes	2	No
ep35	F	36	17	TLE L	2Y	34Y	4–6/mo	Yes	Yes	2	No

Table 1: (Continuation)

ep36	F	32	18	TLE R	27Y	5Y	5-6/mo	Yes	No	2	No
ep37	F	58	12	TLE L	16Y	42Y	2-3/mo	Yes	No	2	No
ep38	M	53	14	TLE L	13Y	40Y	8-10/mo	Yes	Yes	3	No
c01	M	49	15	NA							
c02	F	42	10	NA							
c04	M	48	11	NA							
c06	F	28	11	NA							
c07	F	35	16	NA							
c08	F	53	8	NA							
c09	F	68	6	NA							
c10	M	71	0	NA							
c11	F	25	17	NA							
c12	M	30	8	NA							
c13	M	35	10	NA							
c14	M	25	17	NA							
c15	F	43	10	NA							
c18	F	43	10	NA							
c19	F	29	18	NA							
c21	M	61	10	NA							
c22	M	28	12	NA							
c25	M	21	13	NA							
c27	F	51	12	NA							
c31	F	51	12	NA							

Table 1: presents the demographic and clinical profiles of participants diagnosed with mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-UHS) alongside a control group. The table includes identifiers (Code), gender (Sex), age, years of education (Edu.), affected side of the temporal lobe (Lesion side), age at disease onset (Onset dis), disease duration, seizure frequency per month (Freq), presence of focal lobe seizures (FIAS), focal bilateral tonic-clonic seizures (FBTCS), scale of antiepileptic drugs used (AEDs), and use of benzodiazepines, barbiturates, and phenobarbital (BZD, BARB & PB).

Table 2: Statistics of brain activation during gain condition

Anatomical Region	cluster size	T	mm coordenates		
			x	y	z
Possitive effects					
	26051	8.69	44	22	-12
AH orbitofrontal cortex		5.73	30	16	-12
UH orbitofrontal cortex		8.69	44	22	-12
AH amygdala		5.62	-20	-2	-16
UH amygdala		6.37	18	-4	-14
AH ventral striatum/NAcc		4.22	-16	12	-8
UH ventral striatum/NAcc		4.83	8	10	-4
AH insula		4.57	-38	-2	-4
UH insula		4.08	43	-2	-12
AH caudate		3.80	-12	-2	14
UH caudate		4.03	12	-2	18
AH anterior cingulate cortex		6.18	0	45	12
UH anterior cingulate cortex		7.08	5	44	6
AH medial frontal gyrus		6.09	2	39	34
UH medial frontal gyrus		5.43	6	42	30
AH superior frontal gyrus		5.19	2	34	50
UH superior frontal gyrus		5.03	6	33	52
AH precuneus		5.71	2	-67	30
UH precuneus		5.50	4	-68	30
AH cuneus		6.00	2	-78	30
UH cuneus		5.48	6	-76	32
AH thlamus		3.28	-3	-13	8
UH thlamus		4.45	6	-9	8
AH dorso lateral prefrontal cortex		5.45	-45	40	12
UH dorsolateral prefrontal cortex		4.69	46	40	10
AH inferior parietal lobe		7.25	-40	-66	39
UH inferior parietal lobe		7.76	44	-66	39
AH parahippocampa gyrus		5.63	-18	-2	-16
UH parahippocampa gyrus		5.39	18	0	-16
AH superior temporal gyrus		4.02	-59	-17	6
UH superior temporal gyrus		2.88	62	-16	8
Negative effects					
	6140				
Primary Motor cortex		8.14	44	-6	56
Supplementary Motor Area		7.82	6	-4	58

Peak voxel coordinates, reported in MNI space, along with peak T-values, are provided for each identified cluster. Effects were considered statistically significant at the whole-brain level if they exceeded a voxel-wise threshold of $P < 0.001$ (cluster size $k > 20$ voxels extent) and cluster-level threshold of $P < 0.05$ (uncorrected). Hemispheric localization is denoted as AH, Affected hemisphere; UH, Unaffected hemisphere.

Table 3: Statistics of brain activation during loss condition

Anatomical Region	cluster size	T	mm coordenates		
			x	y	z
Possitive effects					
	24127	9.00	44	22	-12
AH orbitofrontal cortex		4.47	30	16	-12
UH orbitofrontal cortex		9.00	44	22	-12
AH amygdala		4.59	-20	-2	-16
UH amygdala		5.78	18	-4	-14
AH ventral striatum/NAcc		3.03	-16	12	-8
UH ventral striatum/Nacc		4.18	8	10	-4
AH insula		5.52	-38	-2	-4
UH insula		4.15	43	-2	-12
AH caudate		3.84	-12	-2	14
UH caudate		3.74	12	-2	18
AH anterior cingulate cortex		4.78	0	44	6
UH anterior cingulate cortex		5.91	5	44	6
AH medial frontal gyrus		6.41	2	39	34
UH medial frontal gyrus		5.63	6	42	30
AH superior frontal gyrus		5.22	2	34	50
UH superior frontal gyrus		5.05	6	33	52
AH precuneus		4.87	2	-67	30
UH precuneus		5.20	4	-68	30
AH cuneus		5.69	2	-78	30
UH cuneus		5.25	6	-76	32
AH thlamus		3.07	-1	-12	8
UH thlamus		4.39	6	-76	32
AH dorsolateral prefrontal cortex		5.09	-45	40	12
UH dorsolateral prefrontal cortex		4.63	46	40	10
AH inferior parietal lobule		5.83	-40	-66	39
UH inferior parietal lobule		6.97	44	-66	39
AH parahippocampa gyrus		5.26	-18	-2	-16
UH parahippocampa gyrus		4.84	18	0	-16
AH superior temporal gyrus		4.07	-59	-17	6
UH superior temporal gyrus		2.77	62	-16	8
Negative effects					
Primary motor cortex	6228	8.27	44	-6	56
Supplementary motor area		7.42	6	-4	58

Peak voxel coordinates, reported in MNI space, along with peak T-values, are provided for each identified cluster. Effects were considered statistically significant at the whole-brain level if they exceeded a voxel-wise threshold of $P < 0.001$ (cluster size $k > 20$ voxels extent) and cluster-level threshold of $P < 0.05$ (uncorrected). Hemispheric localization is denoted as AH, Affected hemisphere; UH, Unaffected hemisphere.

Table 4: Statistics of brain activation differences in gain condition contrasting Control vs mTLE-UHS

Anatomical Region	cluster size	cluster p(unc)	T	voxel p(unc)	x,y,z {mm}
		Positive effects			
	267	0.004	4.70	0.000	30 4 -16
UH insula			4.49	0.000	44 -2 -6
UH amygdala					
UH superior temporal gyrus			3.45	0.001	18 2 -16
	216	0.008	3.83	0.000	44 18 38
UH DLPFC				0.000	36 20 32

MNI coordinates and T-value for the peak location in a particular identified anatomical cluster. In the control vs. mTLE-UHS contrast, effects were considered statistically significant at the whole-brain level if they exceeded a voxel-wise threshold of $P < 0.001$ (cluster size $k > 20$ voxels extent) and cluster-level threshold of $P < 0.05$ (uncorrected). AH, Affected hemisphere; UH, Unaffected hemisphere; DLPFC, dorsolateral prefrontal cortex.

Table 5: Statistics of brain activation differences in loss condition contrasting Control vs mTLE-UHS

Anatomical Region	cluster size	Cluster p(unc)	T	voxel p(unc)	x,y,z {mm}
		Possitive effects			
	183	0.013	4.31	0.000	30 4 -16
UH insula			4.11	0.000	44 -2 -6
UH amygdala			3.88	0.000	30 4 -18
UH superior temporal gyrus			3.01	0.002	56 -8 -8
	218	0.008	4.14	0.000	44 18 38
UH DLPFC			3.79	0.000	36 20 32
			3.26	0.001	34 8 32
AH SFG	107	0.048	3.94	0.000	0 28 50

MNI coordinates and T-value for the peak location in a particular identified anatomical cluster. Effects were considered statistically significant at the whole-brain level if they exceeded a voxel-wise threshold of $P < 0.001$ (cluster size $k > 20$ voxels extent) and cluster-level threshold of $P < 0.05$ (uncorrected). AH, Affected hemisphere; UH, Unaffected hemisphere; DLPFC, dorsolateral prefrontal cortex; LFSM, left frontal superior medial gyrus.

Table 6: Main effects of gain condition for the interaction of evaluations and groups

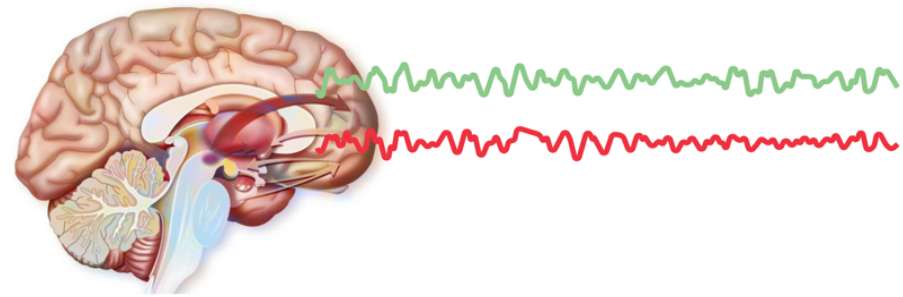
Anatomical region	cluster size	cluster p(unc)	T	voxelp(unc)	x,y,z {mm}
		Positive effects			
AH superior frontal gyrus	168	0.022	4.44	0.000	-6 32 48
AH inferior frontal gyrus	215	0.011	4.32	0.000	-50 14 0
AH superior temporal gyrus			3.73	0.000	-48 12 -12
AH insula			2.92	0.001	-38 16 -8
AH nucleus accumbens	134	0.038	4.05	0.000	-8 16 -2
AH pallidum			3.47	0.000	-10 4 -2
UH middle temporal gyrus		0.025	3.80	0.000	52 -20 -8
UH insula			3.55	0.000	46 -4 -6
UH inferior frontal gyrus	101	0.028	3.61	0.000	44 28 16

MNI coordinates and T-value for the peak location in a particular identified anatomical cluster. Effects were considered statistically significant at the whole-brain level if they exceeded a voxel-wise threshold of $P < 0.001$ (cluster size $k > 20$ voxels extent) and cluster-level threshold of $P < 0.05$ (uncorrected). AH, Affected hemisphere; UH, Unaffected hemisphere.

Table 7: Main effects of loss condition for the interaction of evaluations and groups

Anatomical region	cluster size	clusterp(unc)	T	voxelp(unc)	x,y,z {mm}
		positive effects			
AH superior frontal gyrus	167	0.022	4.34	0.000	-6 32 48
AH inferior frontal gyrus	188	0.016	4.25	0.000	-50 14 0
AH superior temporal gyrus			3.50	0.000	-48 14 -12
AH insula			2.92	0.000	-38 16 -8
AH nucleus accumbens	121	0.047	3.94	0.000	-8 16 -2
AH pallidum			3.41	0.001	-10 4 -4
UH inferior frontal gyrus	103	0.040	3.52	0.000	40 38 6

MNI coordinates and T-value for the peak location in a particular identified anatomical cluster. Effects were considered statistically significant at the whole-brain level if they exceeded a voxel-wise threshold of $P < 0.001$ (cluster size $k > 20$ voxels extent) and cluster-level threshold of $P < 0.05$ (uncorrected). AH, Affected hemisphere; UH, Unaffected hemisphere.



CHAPTER IV: GENERAL DISCUSSION AND CONCLUSIONS

General Discussion

This dissertation explores the complex interplay between cognitive functions and neural circuitry in individuals with mesial temporal lobe epilepsy due to unilateral hippocampal sclerosis (mTLE-UHS). By integrating findings from behavioral assessments, neuropsychological evaluations, electrophysiological investigations, and neuroimaging modalities, this research provides a comprehensive overview of the impact of mTLE-UHS on decision-making and reward processing (RP), both before and after surgical intervention. This discussion synthesizes the key findings, situating them within the broader context of existing investigations and highlighting the clinical implications of these discoveries.

Study 1: Electrophysiological correlates of reward processing in mTLE-UHS

This study used a combination of behavioral tasks [Game of Dice Task (GDT), Iowa Gambling Task (IGT), and a probabilistic gambling task (PGT)] and EEG, identified impairments in decision-making under ambiguity in individuals with mTLE-UHS. This impairment, evident in the IGT, manifested as an increased preference for disadvantageous choices, particularly when decisions relied on information from previous outcomes and are aligned with previous literature (21,25,274,481). Notably, patients' performance on the GDT, which assesses decision-making under risk, did not differ significantly from that of healthy controls (21,273,274). This difference between performance on the IGT and the GDT suggests that the cognitive processes underlying these two types of decision-making may be differently affected in mTLE-UHS.

These behavioral observations were further supported by electrophysiological findings. Patients with mTLE-UHS showed a reduced amplitude of the Feedback-Related Negativity (FRN) component, a neural marker of feedback processing and reinforcement learning (482,483). This reduction, coupled with a weaker effect of emotional valence (loss versus gain) on parietal delta activity and a general reduction of frontal theta activity, indicates a disrupted feedback processing mechanism in mTLE-UHS. The FRN, reflecting dopaminergic signals in the midbrain after unexpected outcomes (484), plays a role in mediating behavioral adjustments and updating expectations based on feedback (485,486). The diminished FRN in mTLE-UHS suggests a compromised ability to

process and use feedback information to guide decision-making, particularly in ambiguous situations (430,431,487,488).

Further analysis of the temporal dynamics of feedback processing revealed a weaker effect of valence on parietal delta activity, accompanied by a general reduction in this frequency range's power. Parietal delta activity, often associated with processing positive feedback and reward anticipation, is critical for learning from feedback and optimizing choice selection (489–492). The weaker valence effect in mTLE-UHS may indicate reduced sensitivity to the rewarding aspects of positive outcomes, potentially contributing to difficulties in learning from rewards and adjusting expectations accordingly (493,494).

Despite these impairments, the study showed a preserved valence effect for frontal theta activity and normal frontal beta-gamma activity in patients with mTLE-UHS. Frontal theta activity, linked to processing negative feedback and the need for behavioral adjustments (495,496), appears to be functionally intact in these patients, suggesting that certain components of the feedback processing system remain unaffected. This difference between impaired parietal delta activity and preserved frontal theta activity highlights the complexity of the neural mechanisms underlying feedback processing and their differential vulnerability in mTLE-UHS.

The study's findings support the notion that mTLE-UHS, while primarily affecting the hippocampus, can cause progressive damage and neural reorganization in interconnected regions and networks (497). This network disruption may contribute to the observed impairments in feedback processing and decision-making under ambiguity (21,25,274,481). In particular, the diminished delta activity associated with the FRN may be linked to disrupted connections between the ventral striatum and other subcortical regions associated with the mesial temporal cortex (498). Conversely, the relative preservation of frontal theta activity, which relies on networks connected with the anterior cingulate cortex (499,500), suggests that this network may be less affected in mTLE-UHS.

Furthermore, the study revealed a significant negative correlation between disease duration and the difference in parietal delta power between gain and loss conditions, suggesting that the progressive disorganization of mesial temporal lobe networks may

worsen the impairments in feedback processing over time (489,501). This observation underscores the importance of early intervention and disease management in mTLE-UHS to mitigate the long-term cognitive and behavioral consequences of the disorder (502,503).

Importantly, the study also assessed the impact of surgical intervention on decision-making and feedback processing in patients with mTLE-UHS. Contrary to initial expectations, the electrophysiological and behavioral measures did not show significant worsening after surgery. This finding suggests that the impaired feedback processing and decision-making under ambiguity observed in mTLE-UHS may be primarily driven by the disease process itself rather than being a consequence of surgical intervention, due the affectation of structures more related with the connections between the ventral striatum and the mesial temporal cortex (504).

In conclusion, Study 1 provides a comprehensive characterization of the impairments in feedback processing and decision-making under ambiguity and risk in individuals with mTLE-UHS. By combining behavioral assessments and electrophysiological investigations, the study elucidates the neural mechanisms underlying these deficits and highlights the differential vulnerability of various components of the reward system in mTLE-UHS. The study also emphasizes the importance of considering the broader cognitive and behavioral implications of the disorder, both pre- and post-surgery, to optimize patient care and improve long-term outcomes.

Study 2: fMRI correlates of reward processing in mTLE-UHS

Study 2 investigated the neural correlates of reward processing in mTLE-UHS patients, using fMRI techniques to assess brain activation patterns during a probabilistic gambling task (monetary). The study compared the fMRI data of patients with a matched control group, during the performance of a probabilistic gambling task, both pre- and post-epilepsy surgery, offering insights into the impact of epilepsy and surgical intervention on brain function.

As expected, mTLE-UHS patients exhibited abnormal brain activation patterns within reward-related circuitry before surgery. Notably, they showed significantly reduced

activity in key areas such as the unaffected hemisphere (UH) insula, amygdala, superior temporal gyrus and DLPFC during both gain and loss conditions, while diminished activation in the Affected hemisphere (AH) superior frontal gyrus was found lonely during loss processing. These regions are important to processing rewards, assigning emotional significance, and regulating cognitive control during decision-making. More precisely, the observed hypoactivation in the UH insula aligns with previous research suggesting that the insular cortex, crucial for integrating sensory and emotional information (505–507), plays a role in processing both positive and negative stimuli (508), potentially contributing to the subjective experience of rewards and aversion (509,510). The diminished insular activity in mTLE-UHS patients may reflect a compromised ability to integrate reward-related information across sensory and emotional modalities, leading to altered decision-making patterns.

Similarly, the reduced activation in the UH amygdala, a region central to emotional processing and the assignment of valence to stimuli (511–513), may underlie the difficulties in emotional regulation and risk assessment observed in mTLE-UHS patients (514). The amygdala is critical for encoding the emotional salience of rewards and punishments, guiding adaptive decision-making in uncertain environments (515).

Furthermore, the diminished activity in the DLPFC, a region implicated in cognitive control, working memory, and decision-making under uncertainty (516–518) suggests broader cognitive impairments beyond reward processing in mTLE-UHS. The DLPFC plays a role in evaluating potential outcomes (519), inhibiting impulsive responses (520), and adapting behavior based on feedback (521), all of which are essential for optimal decision-making (522).

The fact that these alterations were observed in the UH underscores the widespread impact of mTLE-UHS on brain function, extending beyond the focal lesion site. This contralateral phenomenon aligns with evidence from genetic and metabolic studies indicating bilateral cerebral involvement in mTLE (523,524). The diminished interhemispheric connectivity and network disruption commonly observed in mTLE may contribute to these contralateral effects, further complicating the clinical picture (525).

Importantly, the study also investigated the impact of epilepsy surgery on reward processing-related brain activity. Post-surgery, mTLE-UHS patients exhibited increased activation in regions like the AH superior frontal gyrus, inferior frontal gyrus, superior temporal gyrus, insula, ventral striatum/NAcc ,pallidum as well as in the UH inferior frontal gyrus, during both gain and loss processing. While for gain condition this higher activity was also found in the UH medial temporal gyrus and UH insula. This pattern of increased activation may reflect neuroplastic changes (526), potentially representing compensatory mechanisms or a reorganization of functional networks following surgical intervention as has been seen also in other resective surgeries like hemispherectomy (527–529). Importantly, at morphological level these "positive" contralateral and ipsilateral effects have been demonstrated after anterior temporal lobe resection (530).

However, interpreting these post-surgical changes necessitates caution. While increased activation may suggest an adaptive response, it could also indicate less efficient or less specific neural processing. Future studies are needed to investigate the functional consequences of these changes, correlating them with behavioral performance and clinical outcomes to fully understand the impact of surgery on the reward system in mTLE-UHS.

In conclusion, Study 2 demonstrates that mTLE-UHS patients exhibit abnormal brain activation patterns within the reward processing circuitry, both pre- and post-surgery. The observed hypoactivation in key brain regions before surgery suggests a compromised reward system, potentially contributing to the cognitive and emotional challenges observed in this population. The increased activation seen after surgery may reflect neuroplastic changes, but further research is needed to elucidate their functional significance and long-term impact. The study highlights the relationship between mTLE-UHS, surgical intervention, and brain function, underscoring the need for an approach to patient care that addresses not only seizure control but also the broader cognitive and emotional aspects of the disorder.

Findings Integration: multimodal approach of reward processing in mTLE-UHS

The combined findings from Studies 1 and 2 provide a comprehensive view of the cognitive and neural alterations in mTLE-UHS, emphasizing the interplay between

feedback processing, decision-making, and reward circuitry functioning. The behavioral impairments observed in Study 1, particularly the tendency for riskier decisions under ambiguity, are supported by the neuroimaging evidence from Study 2, which revealed hypoactivation in crucial brain regions involved in reward processing and cognitive control (511,531–538). This convergence of findings suggests that mTLE-UHS disrupts the neural circuitry underlying the evaluation of rewards and punishments, hindering adaptive decision-making in uncertain environments (21,25,539).

Moreover, the electrophysiological data from Study 1, showcasing a reduced FRN and diminished delta activity, reinforces the notion of a compromised feedback processing mechanism in mTLE-UHS. These impairments may hinder the ability to learn from both positive and negative outcomes (487,489,540–542), potentially leading to suboptimal decision-making strategies, especially in situations requiring flexible adaptation based on feedback (430,431,488).

The integration of both studies' findings also highlights the critical role of the mesial temporal lobe structures, particularly the hippocampus, in the complex interplay of cognitive functions and neural circuitry (23,543–545). While the focus of damage in mTLE-UHS is the hippocampus, the observed network disruption and functional alterations extend beyond this region, influencing interconnected areas such as the ventral striatum, amygdala, and prefrontal cortex (324,546–550). This highlights the importance of considering the broader network-level effects of mTLE-UHS, rather than focusing solely on the focal lesion site, to fully understand the cognitive and behavioral consequences of the disorder.

Furthermore, the findings from both studies emphasize the need for a nuanced approach to evaluating and treating mTLE-UHS. The observed impairments in feedback processing, decision-making, and reward circuitry functioning underscore the importance of considering the broader neuropsychological impacts of the disorder, including cognitive control, working memory, and emotional regulation, in addition to seizure control.

The stability of neural substrates for processing gains and losses post-surgery, observed in Study 2, offers a promising avenue for future research into adaptive neuroplasticity and

its role in cognitive and emotional recovery. This research direction may lead to more targeted and effective therapeutic strategies aimed at optimizing cognitive and emotional health, potentially enhancing the quality of life for individuals with mTLE-UHS.

Finally, the present research underscores the importance of interdisciplinary collaboration in advancing the understanding and treatment of mTLE-UHS. By integrating perspectives from neurology, neuropsychology, and cognitive neuroscience, this research highlights the complex interplay between brain structure, function, and behavior in this disorder.

Future research directions

Building upon the foundation laid by the present research, future investigations should focus on addressing the limitations encountered and exploring new frontiers in the study of mTLE-UHS and its impact on cognitive function.

Addressing limitations:

- **Larger sample sizes**: A priority is to recruit larger and more diverse patient cohorts to enhance the statistical power and generalizability of findings. This may involve establishing collaborative research networks across multiple epilepsy centers, enabling the collection of data from a broader range of individuals with mTLE-UHS, thus minimizing potential biases related to specific patient profiles or treatment protocols.
- **Connectivity analyses**: Incorporating advanced connectivity analyses in fMRI studies will be crucial to elucidating the neural network changes associated with mTLE-UHS and surgical intervention. Investigating functional and structural connectivity patterns can reveal how different brain regions interact during reward processing and decision-making, providing a more comprehensive view of the neuroplasticity and network reorganization that occur in this disorder.
- **Hemispheric differentiation**: A more refined analysis that considers the laterality of epileptogenic foci and surgical resection is warranted. Separating patients into right versus left mTLE-UHS groups can unveil potential hemispheric differences in the impact of the disorder and surgical intervention on brain function, allowing for a more precise understanding of lateralization effects.

- **More sensitive behavioral tasks**: Exploring and validating alternative behavioral tasks with proven sensitivity for detecting cognitive alterations in mTLE-UHS is crucial. Employing tasks that assess different aspects of decision-making, such as risk aversion, loss aversion, and ambiguity tolerance, can provide a more comprehensive understanding of the behavioral consequences of mTLE-UHS.
- **Assessment of affective states**: Integrating in-depth assessments of mood, anxiety, and anhedonia, both pre- and post-surgery, will offer a more comprehensive view of patients' psychological health and the long-term impacts of surgical intervention. Utilizing validated instruments like the Beck Depression Inventory (BDI) and the Snaith-Hamilton Pleasure Scale (SHAPS) can quantify affective symptoms, enabling a more precise analysis of the interplay between reward processing alterations and emotional well-being.
- **Longitudinal follow-up**: Extending the follow-up period beyond the current three-month post-surgical evaluation is essential to understanding the long-term cognitive and emotional trajectories of mTLE-UHS patients. Conducting neuropsychological and neuroimaging assessments at multiple time points post-surgery can reveal how brain function and cognitive abilities evolve over time, providing valuable insights into the enduring effects of surgical intervention.

Exploring New Frontiers:

- **Investigating the role of specific hippocampal subfields**: Recent advancements in neuroimaging techniques allow for the segmentation and analysis of individual hippocampal subfields. Exploring the differential involvement of these subfields in reward processing and decision-making in mTLE-UHS could provide a more refined understanding of the hippocampal contributions to these cognitive functions.

- **Exploring the Impact of Interictal Epileptiform Discharges (IEDs)**: Investigating the dynamic effects of IEDs on reward circuitry using simultaneous EEG-fMRI can elucidate how these abnormal electrical events disrupt the normal functioning of the reward system, potentially contributing to the observed cognitive and emotional impairments in mTLE-UHS.

- **Developing targeted interventions**: Translating the knowledge gained from research into the development of tailored interventions for mTLE-UHS patients experiencing reward processing and decision-making difficulties is crucial. Exploring pharmacological and non-pharmacological therapies aimed at modulating the reward system and enhancing cognitive control could improve patients' emotional well-being and quality of life.

- **Patient-centered research**: Involving patients in the design and implementation of research studies is vital to ensure that the research questions and outcomes are meaningful and relevant to their experiences and needs. Incorporating patient-reported outcomes can provide valuable insights into the real-world impacts of epilepsy and its treatments.

By embracing these future research directions, the field can continue to advance the understanding of mTLE-UHS and its multifaceted implications. This knowledge will ultimately pave the way for improved patient care and support, fostering a more comprehensive approach to epilepsy management that addresses both seizure control and the broader cognitive, emotional, and social well-being of individuals with this disorder.

Conclusions

This dissertation provides a comprehensive exploration of the intricate relationship between cognitive functions, neural circuitry, and clinical manifestations in individuals with mTLE-UHS. By integrating findings from behavioral assessments, neuropsychological evaluations, electrophysiological investigations, and neuroimaging modalities, this research has elucidated the complex interplay between brain structure, function, and behavior in this disorder. The findings underscore the pervasive impact of mTLE-UHS on cognitive and emotional processing, extending beyond the focal lesion in the hippocampus to encompass broader brain networks involved in reward processing, decision-making.

The study has revealed that individuals with mTLE-UHS exhibit impairments in decision-making under ambiguity, particularly in situations requiring the integration of feedback information to guide choices. This impairment, evident in their performance on the Iowa

Gambling Task, suggests a compromised ability to effectively learn from both positive and negative outcomes, potentially leading to suboptimal decision-making strategies. This finding is further supported by electrophysiological evidence showcasing a reduced FRN amplitude and diminished delta activity, indicating disruptions in the neural mechanisms responsible for feedback processing and reward anticipation.

The neuroimaging findings from the fMRI study complement these observations by revealing distinct patterns of brain activation in mTLE-UHS patients compared to healthy controls. Notably, reduced activity in key regions of the reward circuitry, such as the non-affected insula, amygdala, STG and DLPFC, suggests a compromised reward system that may contribute to the cognitive and emotional challenges observed in these individuals. The observation of contralateral effects, with hypoactivation predominantly observed in the hemisphere opposite the lesion site, highlights the widespread impact of mTLE-UHS on brain function and the potential role of diminished interhemispheric connectivity in these alterations.

Furthermore, the study has shed light on the impact of surgical intervention on reward processing and decision-making in mTLE-UHS. Despite initial expectations, the electrophysiological and behavioral measures did not show significant worsening after surgery, suggesting that the observed cognitive impairments may be primarily driven by the disease process itself rather than being a direct consequence of surgical resection. However, the increased activation observed in certain brain regions post-surgery, such as the affected superior frontal gyrus, insula, and nucleus accumbens, might indicate potential neuroplastic changes that may represent either compensatory mechanisms or a reorganization of functional networks following surgical intervention.

In conclusion, this dissertation underscores the importance of considering the broader neuropsychological impacts of mTLE-UHS, including working memory, and emotional regulation, in addition to seizure control. The findings advocate for a more nuanced and comprehensive approach to patient care, addressing both the immediate challenges posed by seizures and the long-term cognitive and emotional consequences of the disorder. Future research endeavors should focus on expanding the current knowledge base, addressing the limitations encountered, and exploring new frontiers in the field,

ultimately leading to the development of more targeted and effective interventions that improve the overall well-being and quality of life of individuals with mTLE-UHS.

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