7T MRI in epilepsy

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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 30th of April at 09.00 in Belfragesalen, Biomedical Centre, Sölvegatan 19, Lund.

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Abstract:

Background: Drug-resistant epilepsy (DRE) affects up to one-third of individuals with epilepsy, for whom surgery may offer the best chance of seizure freedom. Surgical evaluation relies heavily on MRI to detect structural lesions such as malformations of cortical development (MCD) and hippocampal pathology. Ultra-high field 7 Tesla (7T) MRI provides higher signal-to-noise ratio and thus higher spatial resolution and slightly different tissue contrast than conventional MRI and may improve lesion detection and presurgical assessment.

Methods: This thesis comprises four studies with complementary designs. Paper I is a prospective imaging study examining microstructural differentiation within MCD using 7T tensor-valued diffusion MRI in 13 patients. Paper II is a prospective observational cohort study of 25 patients with MCD, assessing lesion morphology, heterotopia-cortex association, and comparison with prior 3T MRI. Paper III, a retrospective clinical cohort study, included 61 patients with drug-resistant temporal lobe epilepsy (TLE) and evaluated the added diagnostic and clinical value of 7T MRI within the presurgical workflow. Paper IV included 42 individuals with TLE and investigated associations between 7T-derived hippocampal subfield volumes and performance on verbal and non-verbal memory tests.

Results: Diffusion MRI at 7T revealed microstructural heterogeneity within MCD lesions that was not visible on conventional MRI. Structural 7T imaging identified 112 MCD lesions and demonstrated frequent connections between heterotopia and cortex, while also uncovering subtle focal cortical dysplasia that was not appreciated at 3T. In the TLE cohort, 7T MRI added clinically meaningful information in >50% of patients by clarifying ambiguous findings, revealing new lesions, or excluding suspected abnormalities. In Paper IV, memory performance did not differ significantly between left- and right-sided TLE, and hippocampal subfield volumes showed only weak and inconsistent correlations with cognitive measures.

Conclusion: 7T MRI improved the detection, delineation, and microstructural characterization of epileptogenic lesions and provided added value in the presurgical evaluation of focal epilepsy. Although hippocampal subfield volumes at 7T were not strongly associated with memory function, the overall findings support integration of 7T MRI into advanced diagnostic pathways for DRE.

Key words: Epilepsy, 7T MRI, malformations of cortical development, temporal lobe epilepsy.

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MADE IN SWEDEN

To my family whom I cherish above all else

"Οὐδὲν ἱερώτερον ταύτης τῆς νόσου· φύσις γάρ ἐστιν"

"There is nothing sacred about this disease; it is of nature"
Hippocrates

Table of Contents

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List of papers

Paper I

Lampinen, B; **Zampeli, A**; Björkman-Burtscher, IM; Szczepankiewicz, F; Källén, K; Compagno Strandberg, M; Nilsson, M. Tensor-valued diffusion MRI differentiates cortex and white matter in malformations of cortical development associated with epilepsy. *Epilepsia*. 2020;61:1701–1713.

Paper II

Zampeli A; Hansson B; Markenroth Bloch K; Englund E; Källén K; Compagno Strandberg M; Björkman-Burtscher IM. Structural association between heterotopia and cortical lesions visualised with 7 T MRI in patients with focal epilepsy. *Seizure*. 2022;101:177-183.

Paper III

Zampeli A; Malac M; Björkman-Burtscher IM; Hansson B; Wennberg L; Markenroth Bloch K; Källen K; Compagno Strandberg M. Does 7 T MRI offer an added value in drug resistant temporal lobe epilepsy? *Seizure.* 2026; 134:27-36.

Zampeli A; Malac M; Björkman-Burtscher IM; Hansson B; Wennberg L; Markenroth Bloch K; Källen K; Compagno Strandberg M. Corrigendum to "Does 7 T MRI offer an added value in drug resistant temporal lobe epilepsy?" [Seizure: European Journal of Epilepsy 134 (2026) 27–36]. *Seizure.* 2026; 136:76

Paper IV

Ljung H; **Zampeli A**; Källén K; Malac M; Björkman-Burtscher IM; Compagno Strandberg M. Hippocampal Subregion–Memory Relationships in Temporal Lobe Epilepsy at 7 T. Manuscript.

Author's contribution to the papers

Paper I

Doctoral student contributed to patient recruitment and selection, collection and description of clinical data, and revision of manuscript.

Paper II

Doctoral student performed the study conduction, data analysis, writing and revision of the manuscript. Doctoral student submitted the paper and contributed to writing the response to the reviewers.

Paper III

Doctoral student performed the study conduction, data analysis, writing and revision of the manuscript. Doctoral student submitted the paper and contributed to writing the response to the reviewers.

Paper IV

Doctoral student performed the study conduction, data analysis and writing the manuscript.

Abbreviations

ATL	Anterior Temporal Lobectomy
DBS	Deep Brain Stimulation
DG	Dentate Gyrus
dMRI	Diffusion MRI
DWI	Diffusion-Weighted Imaging
DRE	Drug-Resistant Epilepsy
EEG	Electroencephalography
FA	Fractional Anisotropy
FLAIR	Fluid-Attenuated Inversion Recovery
FCD	Focal Cortical Dysplasia
fMRI	functional MRI
GMH	Grey Matter Heterotopia
HS	Hippocampal Sclerosis
MCD	Malformations of Cortical Development
MTLE	Mesial Temporal Lobe Epilepsy
MKa	Microscopic Kurtosis Anisotropy
MEG	Magnetic Electroencephalography
MRI	Magnetic Resonance Imaging
PVNH	Periventricular Nodular Heterotopia
PET	Positron emission tomography
RF	Radiofrequency
SAH	Selective Amygdalohippocampectomy
SNR	Signal to Noise Ratio
SBH	Subcortical Band Heterotopia
SWI	Susceptibility-weighted imaging
TLE	Temporal Lobe Epilepsy
UHF	Ultra-high field
VNS	Vagus Nerve Stimulation

Introduction

Epilepsy

Epilepsy epidemiology

Epilepsy is among the most widespread neurological conditions, touching the lives of tens of millions of people across all ages and regions. Recent estimates from the 2021 Global Burden of Disease Study indicate that approximately 51.7 million individuals were living with epilepsy worldwide, corresponding to an age-adjusted prevalence of about 658 per 100 000 population. Roughly half of these cases were classified as idiopathic, while the remainder were attributed to identifiable structural, genetic, infectious, or metabolic causes (1).

Incidence varies considerably across regions and levels of economic development. A meta-analysis reported a global pooled incidence of about 50.4 per 100 000, with rates tending to be lower in high-income settings (approximately 45 per 100 000) and substantially higher in low- and middle-income countries, where estimates can reach well above 200 per 100 000 (2). Another systematic review found a lifetime prevalence of 7.6 per 1 000 individuals and an active epilepsy point prevalence of 6.4 per 1 000, with an annual incidence of about 61 per 100 000 person-years (3).

These numbers highlight a persistent global imbalance. More than 80% of people with epilepsy live in low- and middle-income regions, where higher disease frequency intersects with limited access to diagnostic tools and long-term treatment. The burden among children and adolescents is particularly striking: in Africa, pooled incidence in this age group has been estimated at approximately 139 per 100 000, compared with approximately 49 per 100 000 in high-income countries (4).

Mortality associated with epilepsy also remains substantial. In 2021, the global age-standardized mortality rate was estimated at approximately 1.74 per 100 000, with consistently higher rates among men (5). Premature mortality is most pronounced in younger individuals, in those with structural or metabolic etiologies, in patients experiencing ongoing convulsive seizures, and in regions where access to timely care is limited (6).

Epilepsy classification

Epilepsy encompasses a broad spectrum of neurological conditions, unified by an persisting tendency to generate recurrent, unprovoked seizures (7, 8). To bring order to this heterogeneity, the International League Against Epilepsy (ILAE) provides a structured framework that categorizes seizures primarily by their onset; focal, generalized, or of unknown origin (**Figure 1**) (9, 10). Beyond seizure onset, epilepsies are further organized according to etiology; genetic, structural, metabolic, immune, infectious, or of unknown cause, and by recognizable epilepsy syndromes, which together support a consistent approach to diagnosis and clinical decision-making (9, 11).

The classification has evolved with each revision aiming to reflect emerging insights into genetic contributions, structural substrates, and developmental influences on epileptogenesis. These refinements promote better communication between clinicians and researchers and ensure that terminology remains aligned with contemporary scientific understanding (11, 12). Although the ILAE framework forms the foundation of current practice, complementary perspectives that incorporate developmental trajectories, genetic findings, and environmental influences continue to enrich our understanding of epilepsy across diverse patient groups (11).

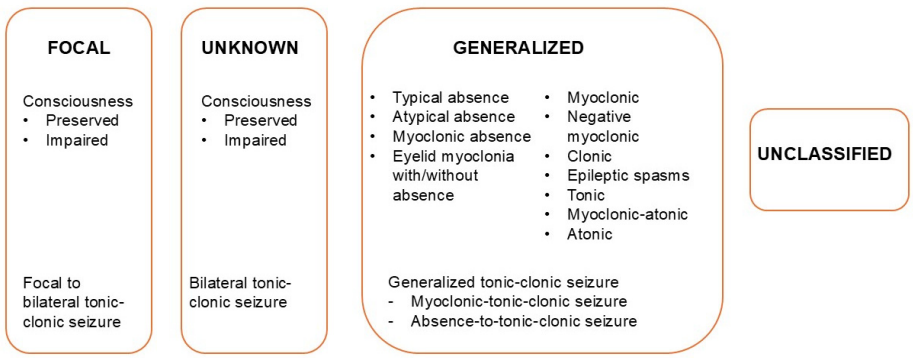

Figure 1. Updated seizure classification according to ILAE.

Malformations of cortical development

Malformations of cortical development (MCD) encompass a diverse group of congenital disturbances affecting the formation of the cerebral cortex. They arise from disruptions in key developmental processes including neuronal and glial proliferation, migration, and cortical organization, and give rise to a wide range of structural anomalies such as grey matter heterotopia (GMH) and focal cortical dysplasia (FCD) (**Figure 2**). These conditions constitute a major cause of

developmental delay, intellectual disability, and epilepsy, and are estimated to account for up to 40% of drug-resistant epilepsy (DRE) cases (13-15). Clinical manifestations vary greatly: while some children experience profound neurological impairment early in life, others present later with epilepsy or more subtle cognitive or motor difficulties (16). This variability illustrates both the biological complexity of MCD and the diagnostic challenges they pose in routine clinical practice.

Over the past decades, neuroimaging has fundamentally improved the detection and characterization of cortical malformations. High-resolution magnetic resonance imaging (MRI) enables detailed assessment of cortical architecture, facilitating identification of subtle abnormalities and clearer delineation of their anatomical extent and relationship to surrounding structures (17).

At the same time, increasing access to genetic testing has provided deeper insight into the molecular mechanisms that drive these malformations. Many forms of MCD stem from de novo or somatic mutations that disrupt pathways essential for cortical development. A good example is the mTOR signaling cascade, which has been implicated in several MCD phenotypes and underscores how dysregulated cell growth and differentiation can alter cortical formation (18). Despite these advances, establishing clear genotype-phenotype relationships remains difficult, reflecting the genetic heterogeneity of MCD.

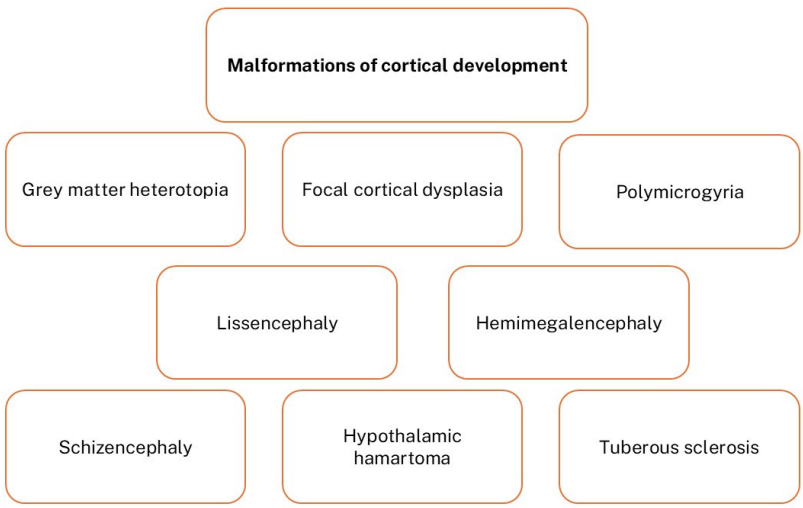

Figure 2. Illustration of the most common malformations of cortical development.

Grey matter heterotopia

Grey matter heterotopia (**Figure 3)** constitutes a distinct group within the MCD, arising when neurons fail to complete their migration to the cortical plate and instead settle in aberrant locations (14, 19). The most frequently encountered forms include periventricular nodular heterotopia (PVNH), subcortical heterotopia, and subcortical band heterotopia (SBH, or "double cortex"), each displaying characteristic imaging patterns and clinical profiles (14, 20). With the improved spatial resolution of modern 3T MRI, the phenotypic spectrum of these entities has broadened, revealing additional features, such as the "transmantle band sign" in PVNH, that may point toward associated cortical abnormalities (21).

Genetically, Filamin A (FLNA) mutations are the hallmark of X-linked PVNH, most identified in females. These cases often show contiguous nodules along the ventricular walls and may coexist with connective tissue, vascular, or cardiac abnormalities (19, 22, 23). Mutations in Doublecortin (DCX) gene, by contrast, are strongly linked to SBH: heterozygous females typically develop the characteristic "double cortex," whereas hemizygous males usually present with a lissencephaly phenotype due to more severe migrational disruption (24, 25).

Epilepsy is the predominant clinical presentation across GMH, frequently with an onset in adolescence or early adulthood and often demonstrating resistance to antiseizure medication (ASM) (26). Cognitive outcomes vary substantially. Individuals with focal PVNH may retain normal intellectual function, whereas those with bilateral or extensive PVNH or with SBH commonly exhibit varying degrees of intellectual disability (27).

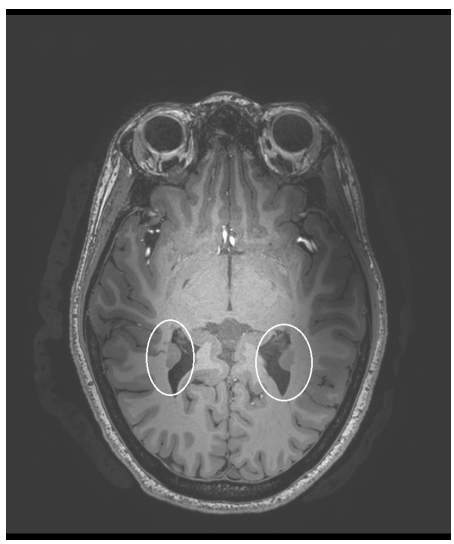

Figure 3. Gray matter heterotopia at 7T MRI. Periventricular heterotopia visualized with T1-weighted (T1w) images.

Focal cortical dysplasia

Focal cortical dysplasia represents a broad spectrum within the MCD group, being among the most frequent structural causes of DRE, particularly in children and young adults, and frequently present diagnostic and therapeutic challenges (28, 29).

On MRI, FCD typically manifests with cortical thickening, blurring of the gray-white matter junction, and, in some cases, the characteristic transmantle sign, which suggests involvement extending from the ventricular surface toward the cortex (**Figure 4**) (30).

Histopathological classification distinguishes three major FCD subtypes (29):

- **Type I (FCD I)** features mild cortical disorganization, often with subtle abnormalities in lamination, microcolumnar arrangements, or irregularities in local cell density, but without distinct cytological changes.
- **Type II (FCD II)** shows more severe cytoarchitectural disruption and is divided into subtypes IIa, with dysmorphic neurons but no balloon cells, and IIb, where dysmorphic neurons coexist with balloon cells. Dysmorphic neurons are enlarged and atypical in both size and orientation, whereas balloon cells are pale, voluminous cells with eccentric nuclei, often interpreted as reflecting arrested or abnormal developmental trajectories. Changes in the underlying white matter such as altered myelination or disordered oligodendroglial patterns are frequently observed. FCD II remains the most common subtype identified in surgical series (31).
- **Type III (FCD III)** refers to cortical dysplasia associated with another principal lesion in the same region, such as hippocampal sclerosis (IIIa), glioneuronal tumors (IIIb), vascular malformations (IIIc), or other cortex-based abnormalities, such as stroke (IIId).

In recent years, substantial progress has been made in clarifying the genetic basis of FCD, particularly type II. Somatic variants affecting components of the mechanistic Target of Rapamycin (mTOR) signaling cascade, including *mTOR*, *DEPDC5*, and *TSC1/TSC2*, have emerged as important drivers of dysplasia. Hyperactivation of this pathway disturbs the normal processes of neuronal differentiation and migration, ultimately producing the characteristic abnormalities in cortical architecture (32, 33).

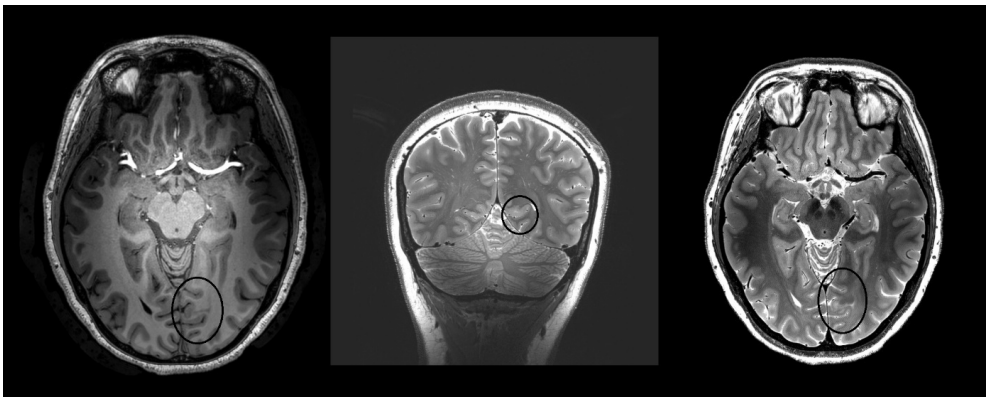

Figure 4. Focal cortical dysplasia at 7T MRI. Focal cortical dysplasia demonstrated on axial T1-weighted images (left), coronal T2-weighted images (middle), and axial FLAIR images (right). Subtle cortical thickening and blurring of the gray–white matter junction are best appreciated on the T2-weighted and FLAIR images.

Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy and represents the leading indication for epilepsy surgery (34). Clinically and anatomically, it is broadly divided into mesial TLE (mTLE) - affecting structures such as the hippocampus, amygdala, and related limbic networks - and lateral or neocortical TLE, which involves the temporal neocortex. Among these, mTLE associated with hippocampal sclerosis (HS) is by far the predominant subtype and has been described extensively from both neuropathological and clinical perspectives (35, 36).

The underlying causes of TLE are diverse. HS is the most frequently identified etiology, but other causes include dual pathology (for example, coexisting FCD), encephaloceles, low-grade tumors, and various MCD. Initial precipitating injuries such as prolonged febrile seizures or central nervous system infections are well recognized in some patients, and genetic predisposition is increasingly acknowledged as playing a role in vulnerability to TLE (35, 37, 38).

Clinically, TLE often presents with focal seizures with impaired awareness, frequently preceded by characteristic auras including visceral sensations, emotional experiences such as fear, or more sensory phenomena. These seizures may progress to bilateral tonic-clonic activity, particularly in longstanding or untreated disease (39).

Despite advances in ASM, a substantial proportion of individuals with TLE develop DRE, and for these patients, surgical intervention remains the most effective treatment option. Long-term seizure freedom is achieved in roughly 60–70% of cases, particularly when HS is present, and resection can be tailored appropriately

(40). Favorable prognostic factors include early surgical referral, clear imaging evidence of HS, absence of dual pathology, and complete resection of the epileptogenic zone - defined as the area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures (41, 42).

For patients who are not candidates for resective surgery, alternative treatments such as deep brain stimulation (DBS) and responsive neurostimulation have gained increasing prominence and now form an important part of the therapeutic landscape for drug-resistant TLE (43).

Hippocampal sclerosis

Hippocampal sclerosis (**Figure 5**) remains the most frequent pathological substrate in mTLE and often defines the group of patients most likely to benefit from surgical treatment. Histologically, HS is marked by selective neuronal loss and reactive gliosis, typically involving the cornu ammonis 1 (CA1) and CA4 (hilus) subfields, and it may be accompanied by granule cell dispersion in the dentate gyrus (DG) (44). The International League Against Epilepsy (ILAE) classification distinguishes three histopathological subtypes: Type 1, which characterized by combined CA1 and CA4 neuronal loss; Type 2, involving predominantly CA1; and Type 3, affecting mainly CA4 (45, 46).

Longitudinal imaging findings have strengthened the link between early-life insults and later HS. In the FEBSTAT cohort, acute hippocampal T2 hyperintensity following febrile status epilepticus in infancy emerged as a strong predictor of later hippocampal atrophy and the development of HS. A substantial proportion of infants with this acute MRI abnormality went on to show definite HS at ten-year follow-up (47, 48).

Advances in neuroimaging have significantly improved the detection of HS, particularly when structural abnormalities are subtle. Automated volumetric and signal-based systems such as the interpretable AID-HS pipeline combine multiple imaging features, including hippocampal volume loss, surface and shape metrics, and signal changes, to identify pathology that may escape visual inspection. Notably, these approaches have demonstrated the ability to detect HS in a large proportion of patients previously considered MRI-negative and can correctly lateralize the affected side in more than 90% of cases (49).

From a prognostic perspective, HS consistently emerges as a favorable factor for long-term seizure freedom. Large surgical cohorts demonstrate that patients with unilateral HS - particularly Type 1 - and those with shorter disease duration and concordant presurgical findings tend to achieve the best outcomes (41, 50).

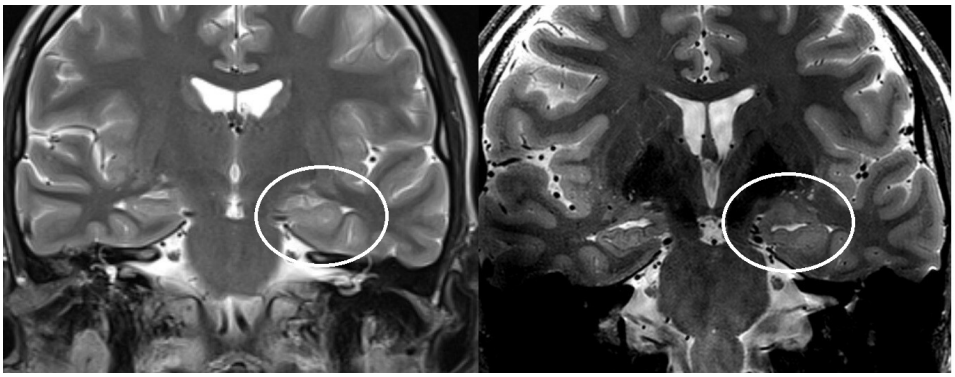

Figure 5. Hippocampal sclerosis demonstrated on coronal T2-weighted 3T MRI (left) 7T MRI (right). Hippocampal volume loss and increased signal intensity are visible on both images, with improved lesion conspicuity and delineation on the 7T image.

Epilepsy surgery

Epilepsy surgery is an established and effective treatment for selected patients with DRE, offering the highest likelihood of long-term seizure freedom when the brain region responsible for seizure generation can be accurately localized and safely resected. Long-term seizure freedom rates are highest when a clear structural substrate can be identified and completely removed (40, 51).

In clinical practice, the goal of presurgical evaluation is to identify the brain region that is indispensable for seizure generation and that can be removed without causing unacceptable neurological deficits. This concept has traditionally been described as the epileptogenic zone, defined as the area of cortex that is necessary and sufficient for initiating seizures and whose removal results in seizure freedom (52). Because this region cannot be directly visualized or measured, it must be inferred from the convergence of multiple sources of information.

Presurgical assessment therefore relies on a multimodal approach. Seizure semiology provides important clues regarding symptom onset and propagation, while scalp electroencephalography (EEG) and, when necessary, invasive recordings contribute crucial information about seizure onset and spatial distribution (52).

Modalities such as magnetoencephalography (MEG) may further refine localization in selected cases (53). Structural and functional imaging play a central role in this process. High-resolution MRI, together with advanced structural sequences and post-processing techniques, has increased sensitivity for detecting subtle or previously unrecognized dysplastic regions (13, 54).

Functional imaging modalities such as fluorodeoxyglucose PET (FDG-PET) provide important complementary information, particularly when structural abnormalities are inconspicuous or located near eloquent cortex (55-57).

In addition, single-photon emission computed tomography (SPECT) and MR spectroscopy may offer further insight into metabolic or perfusion-related abnormalities. Today, presurgical evaluation relies on the multimodal integration of structural and functional imaging to localize the brain region most closely associated with seizure onset, especially in cases where conventional MRI does not reveal clear pathology (58).

While concordant findings across modalities may allow relatively confident localization in many patients, the presurgical process is not always straightforward. In cases where imaging, electrophysiology, and clinical features are discordant, additional investigations may be required, often including invasive EEG monitoring. Such stepwise hypothesis testing reflects the fact that the epileptogenic zone remains a theoretical construct rather than a directly observable entity (52).

The likelihood of surgical success is closely linked to the accuracy with which this region can be defined and completely resected. When a well-delineated structural lesion corresponds with electroclinical findings, seizure freedom rates are generally higher (40, 51). In contrast, when no clear lesion is identified or when abnormalities appear subtle or multifocal, both localization and outcome prediction become more uncertain (58).

These challenges underscore the importance of careful multidisciplinary evaluation. Surgical decisions are made through the integration of clinical, electrophysiological, and imaging data, balancing the potential for seizure freedom against the risk of functional impairment.

Surgical approaches and long-term outcomes

Among surgical strategies, anteromesial temporal lobectomy (ATL) remains the standard approach and consistently achieves the highest rates of seizure freedom. Comparative data suggest that ATL outperforms selective amygdalohippo-campectomy (SAH), with seizure-free rates of approximately 79% versus 67% (59). Although SAH may be preferred in some surgical philosophies for its theoretical preservation of cognitive function, its' benefit in seizure control appears modestly lower.

Long-term evolution of surgical outcomes is an important consideration for patients and clinicians. In a large adult cohort from 2009, Engel Class I rates were 76% at 6 months post-surgery, 72% at 2-5 years, and 70% at 10-15 years, demonstrating that once seizure freedom is achieved early, it tends to persist (60).

Multiple clinical and electrophysiological factors contribute to postoperative prognosis. Favorable predictors include the presence of a lesional abnormality on

MRI (particularly HS) unilateral interictal EEG discharges, concordant seizure semiology, shorter epilepsy duration before surgery, younger age at the time of surgery, and complete resection of the epileptogenic zone.

Patients with MRI-negative epilepsy experience significantly lower rates of seizure freedom, typically around 40-50% after temporal resections and 20-25% following extratemporal procedures. These cases emphasize the importance of a comprehensive presurgical evaluation incorporating PET, SPECT, MEG, and even MRI post-processing to identify subtle lesions that may not be apparent on routine imaging (61, 62).

Histopathology also plays a key role. Individuals with FCD (particularly type II) generally achieve more favorable outcomes than those with nonspecific gliosis or normal histopathology (63). Epilepsy associated with low-grade tumors shows especially good prognosis, with complete resection resulting in seizure freedom in more than 80% of cases (64).

Minimally invasive procedures

Minimally invasive surgical options have become increasingly relevant. Laser interstitial thermal therapy (LITT) is now widely used, particularly for mTLE, and offers a less invasive alternative for patients who may not be ideal candidates for open resection. Reported Engel Class I outcomes range from 55% to 60%. Cognitive morbidity appears lower compared with ATL or SAH, although long-term durability of seizure control continues to be evaluated (65).

Neuromodulation techniques

When resection or ablation is not feasible due to bilateral seizure onset, eloquent cortex involvement, or distributed epileptogenic networks, neuromodulation represents an essential therapeutic option. Vagus nerve stimulation (VNS), in use for more than 30 years, demonstrates gradual improvement in seizure control with time, with responder rates - defined as a ≥50% reduction in seizure frequency- reaching 50-60% (66).

Another modulation technique, DBS most often targeting the anterior nucleus of the thalamus, produces average seizure reductions of approximately 55-60%, with two-thirds of patients achieving responder status (67). Responsive neurostimulation (RNS), which delivers closed-loop stimulation in response to detected epileptiform activity, shows similar or slightly higher effectiveness, with seizure reductions frequently exceeding 60% and responder rates around 70% on long-term follow-up (67, 68). The technique is though not yet approved for clinical use in Europe.

Neuromodulation is increasingly used in pediatric patients as well. Evidence indicates that more than 70% achieve at least a 50% reduction in seizure frequency, and a subset become seizure-free (69).

Neuroimaging

MRI basics

Magnetic Resonance Imaging is a non-invasive technique that provides detailed anatomical images of the brain without exposing patients to ionizing radiation. Its value in epilepsy lies in its ability to visualize subtle abnormalities in cortical and subcortical structures with high spatial resolution. MRI is based on the magnetic properties of hydrogen protons, which are abundant in biological tissue. When placed in a strong magnetic field, the spins of these protons partially align with the field, producing a longitudinal magnetization. A radiofrequency (RF) pulse temporarily perturbs this equilibrium by tipping the magnetization into the transverse plane, where it precesses and induces a signal in receiver coils. This signal is then reconstructed into cross-sectional brain images (70).

The MRI contrast is largely determined by the relaxation properties of the tissue, which governs how rapidly protons recover longitudinal magnetization (T1 relaxation) and how quickly transverse magnetization decays due to spin dephasing (T2 relaxation). Contrast weighting towards these mechanisms can be adjusted through sequence parameters. T1-weighted images provide high anatomical detail, with white matter appearing brighter than gray matter in adult patients and are particularly valuable for assessing structure such as the hippocampus and the temporal neocortex. T2-weighted and FLAIR sequences highlight tissue with increased water content and therefore excel at detecting pathology; gliosis, edema, inflammation, or cortical malformations (71, 72).

Epilepsy-dedicated MRI protocols are designed to maximize the sensitivity for detecting subtle abnormalities. Thin coronal slices aligned with the hippocampal axis, high-resolution 3D sequences, and optimized FLAIR imaging enable careful assessment of mesial temporal structures as well as FCD in the neocortex. Additional techniques such as susceptibility-weighted imaging (SWI) can reveal microhemorrhages, venous anomalies, or cavernous malformations that may contribute to seizure onset (71, 73).

Because MRI avoids ionizing radiation, it is well suited for repeated examinations across the course of evaluation and treatment. Serial imaging can document the evolution of DRE, monitor postoperative changes, and detect recurrence or new pathology when clinically indicated. This makes MRI a central component of long-term management in patients undergoing both medical and surgical care for epilepsy (73).

7T MRI

Ultra-high field (UHF) magnetic resonance imaging at 7 Tesla (7T) represents a major advance beyond conventional 1.5T and 3T systems. A higher signal-to-noise ratio enables a higher spatial resolution and larger inter-tissue differences in T1 relaxation enhance the structural contrast. (74). This enables visualization of fine anatomical details that are difficult to resolve at lower field strengths including hippocampal subfields, small brainstem nuclei, cortical lamination, and subtle vascular or white matter abnormalities (75-77).

The higher field strength also enables the use of imaging techniques that benefit from increased susceptibility effects, including high-resolution T2*, SWI, and quantitative susceptibility mapping. These approaches provide additional information on tissue composition, iron deposition, and microvascular architecture, extending the scope of structural and microstructural assessment (78, 79).

At the same time, the transition from 3T to 7T brings technical challenges. Higher field strengths increase RF field inhomogeneity, elevate specific absorption rates, and make images more susceptible to distortion, especially near air-tissue interfaces. These limitations have stimulated substantial advances in hardware and pulse sequence design, including the use of multi-channel transmit-receive arrays, parallel transmission, and tailored RF pulses to stabilize image quality (80, 81).

Patient comfort and safety remain important considerations. Some individuals experience transient dizziness, vertigo, metallic taste, or mild headache, during exposure to UHF, although such effects typically lessen with repeated scans (82). Despite these challenges, 7T MRI (**Figure 6**) is steadily becoming integrated into clinical workflows and advanced research protocols (54, 83-86).

Figure 6. 7T MRI scanner installed in Lund in October 2015, by Lund University Bioimaging Center.

7T MRI in epilepsy

In epilepsy, the enhanced spatial resolution of 7T MRI is particularly valuable for identifying subtle structural abnormalities that may remain undetected on conventional imaging. This is especially relevant in patients with drug-resistant focal epilepsy, where accurate identification of the epileptogenic substrate is critical for successful surgical treatment. Several studies have shown that a proportion of patients considered MRI-negative at 3T demonstrate detectable abnormalities when examined at 7T (54, 83-86).

UHF imaging has shown particular benefit in the evaluation of FCD, HS, and other MCD, where increased resolution improves lesion conspicuity and anatomical delineation (83, 86).

Technical developments have further strengthened the clinical utility of 7T MRI in epilepsy. Parallel transmit (pTx) systems, for example, help counteract B1-field inhomogeneity and reduce regional signal loss, an issue especially relevant for imaging within the temporal lobes. These refinements have contributed to more consistent image quality and more reliable assessment of structures that are central to presurgical evaluation (87).

In the presurgical setting, 7T MRI provides clearer delineation of lesion borders and finer anatomical detail, which can facilitate the integration of imaging with electrophysiological recordings and other functional datasets. This closer correspondence between structural and functional information supports more precise surgical planning and enhances the likelihood of identifying the true epileptogenic zone.

The introduction of the 7T Epilepsy Task Force consensus protocol (88) has accelerated clinical adoption by standardizing acquisition parameters and ensuring that scans are optimized for epilepsy-specific needs. The protocol, incorporating high-contrast 3D T1-weighted, submillimeter 3D FLAIR, T2-weighted and susceptibility-based imaging, and dedicated sequences for hippocampal and cortical subfields, has shown clear diagnostic value. Studies applying this framework report improved lesion conspicuity compared with 3T MRI and confirm that structured 7T protocols can be incorporated effectively into comprehensive presurgical workflows (84, 85).

Diffusion MRI

Diffusion magnetic resonance imaging (dMRI) is a non-invasive method that captures the random motion of water molecules within biological tissues, offering valuable information about microstructural organization. In the central nervous system, this approach is particularly informative for assessing white matter, where water diffusion is directionally constrained by axonal membranes and myelin sheaths. Because diffusion occurs more readily along the axis of fiber bundles than perpendicular to them, the resulting anisotropy can be quantified using diffusion tensor imaging and measures such as fractional anisotropy (FA), which reflects the overall degree of directional diffusion within a voxel (89).

Although the FA has become a standard marker of white matter integrity, it is an unspecific metric that is influenced by many properties including fiber orientation, crossing fibers, and partial volume effects. As a result, it cannot fully distinguish microstructural properties such as the shape of individual tissue components. To address these limitations, advanced diffusion methods such as double diffusion encoding and diffusion encoding using free waveforms have been developed. These techniques yield metrics such as microscopic anisotropy (MKa), which characterize microscopic diffusion anisotropy independently of orientation dispersion (90).

By disentangling the shape of microscopic structures from their dispersion in orientations and isolating microscopic anisotropy, the MKa provides more precise information on tissue microstructure than the conventional FA. It has shown strong associations with cellular features such as axonal density and fiber integrity and remains robust even in regions with complex fiber configurations. This increased specificity has raised interest in MKa as a potential biomarker in clinical research. Alterations in microscopic anisotropy have been documented across a range of neurological disorders, including multiple sclerosis, stroke, brain tumors, and epilepsy, suggesting that MKa may help detect early or subtle microstructural changes that are not visible on standard imaging or traditional diffusion tensor imaging (91, 92).

Diffusion MRI in epilepsy

In epilepsy, dMRI has consistently revealed microstructural abnormalities that extend beyond lesions visible on conventional structural imaging. Reduced FA is commonly observed in patients with TLE, not only within the epileptogenic temporal lobe but also in extratemporal white matter pathways. These findings suggest that epilepsy involves distributed network alterations rather than strictly focal pathology (93, 94).

Diffusion abnormalities have been associated with several clinical factors, including epilepsy duration, seizure frequency, and age at seizure onset, supporting their relevance as markers of disease burden and progression (95). In patients with MRI-negative epilepsy, dMRI can identify subtle white matter alterations that are not apparent on conventional imaging, providing complementary information for localization of the epileptogenic network (96).

More advanced diffusion metrics have further refined the characterization of epilepsy-related microstructural changes. Reductions in MKa have been reported in hippocampal and white matter regions in TLE, indicating alterations in tissue organization even in regions with complex fiber architecture that would confound metrics such as the FA (97). Combining conventional diffusion measures with advanced microstructural metrics may therefore improve sensitivity to epilepsy-related abnormalities, particularly in patients without a clearly visible lesion on standard MRI.

Hippocampal segmentation

The hippocampus, though small in size, has a remarkably intricate internal architecture that supports memory, emotional processing, and spatial navigation. Its subregions; the CA1-CA4 fields, DG, and subiculum, possess different cellular compositions and functional roles, features that become especially relevant in TLE

(26). Among these, CA1 stands out for its selective vulnerability: it is particularly prone to hypoxic-ischemic injury and often shows the most pronounced neuronal loss and gliosis in HS, reflecting its sensitivity to metabolic stress and excitotoxicity (98, 99). In contrast, CA3 and the DG, with their dense recurrent excitatory circuits contribute to the network plasticity that may facilitate both adaptive processes and epileptogenesis. (100). The subiculum functions as the primary output region of the hippocampal formation, relaying processed information to the entorhinal cortex, amygdala, thalamus, and other widespread targets; its strategic position explains why structural compromise can affect memory and broader cognitive functions (101, 102).

The development of high-resolution MRI, especially at 7T, has made it increasingly possible to distinguish these subfields in vivo. Hippocampal segmentation methods aim to translate the underlying anatomy into reproducible MRI-based labels, offering greater specificity than global volumetric measures. Manual segmentation following histologically derived landmarks remains the most anatomically faithful approach, though its labor-intensive and operator-dependent nature limits routine use. Automated tools such as FreeSurfer and automatic segmentation of hippocampal subfields (ASHS) have therefore become widely adopted. FreeSurfer applies probabilistic atlases built from ex vivo MRI and histology, whereas ASHS uses multi-atlas label fusion combined with machine-learning techniques to achieve higher precision, particularly at field strengths that capture fine-grained laminar detail (103, 104).

In epilepsy, subfield segmentation (**Figure 7**) has proven especially valuable for identifying subtle or focal forms of hippocampal sclerosis that may escape detection on standard visual inspection. High-field MRI studies consistently show that atrophy in CA1 and the DG is among the earliest and most prominent markers, while relative preservation of CA2 or the subiculum may help distinguish among ILAE-defined subtypes of sclerosis (105-107). Importantly, automated volumetric findings have been validated against surgical histopathology, demonstrating that MRI-derived patterns correspond well to neuronal loss and gliosis in resected tissue (105). Subfield-specific measures have also been linked to clinical features such as epilepsy duration, seizure burden, and memory performance, and may improve the prediction of postoperative cognitive outcomes, especially in patients undergoing temporal lobe resections (108).

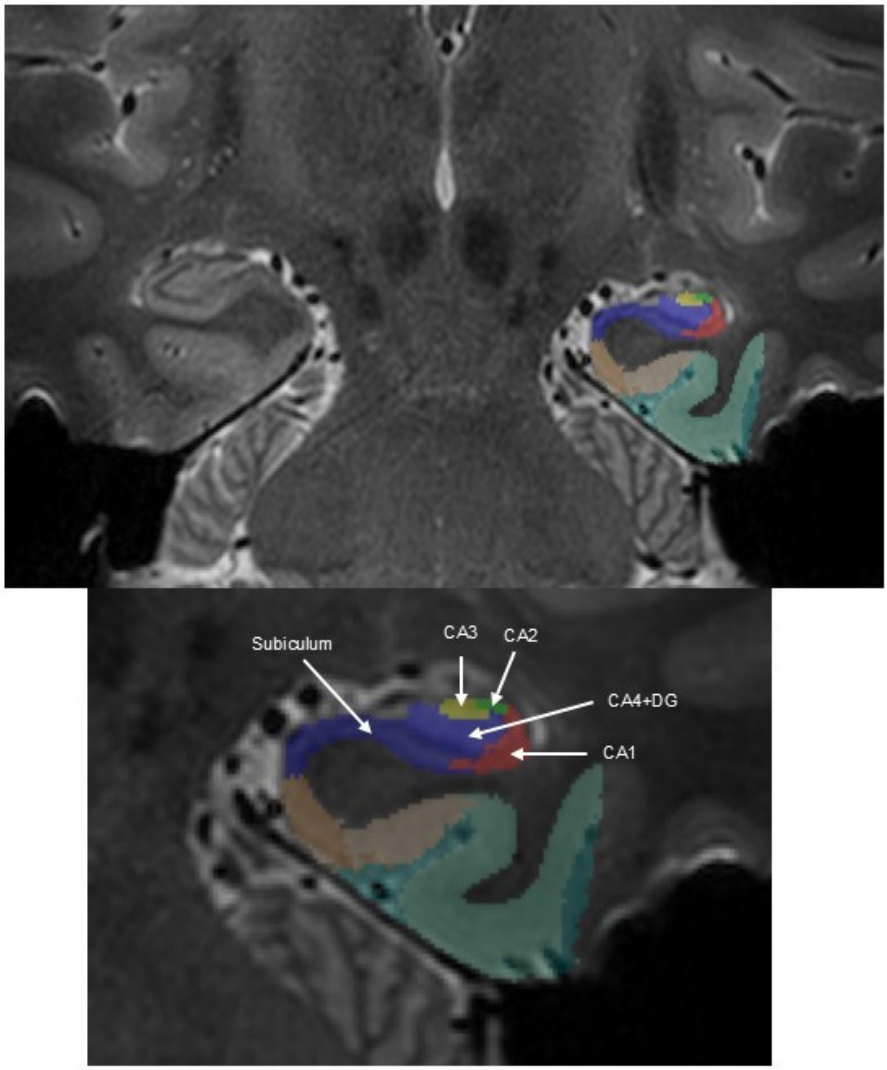

Figure 7. Hippocampal segmentation illustrated on coronal T2-weighted 7T MRI. The hippocampus is clearly delineated and subdivided into its anatomical subfields, displayed using color coding. The segmentation includes CA1, CA2, CA3, CA4/dentade gyrus (DG) and the Subiculum. The high tissue contrast of T2-weighted images enables reliable visualization of internal hippocampal architecture and subfield boundaries.

Clinical value of 7T MRI

The clinical value of 7T MRI lies primarily in its ability to detect and characterize structural abnormalities that are difficult to visualize at conventional field strengths. By providing higher spatial resolution and improved tissue contrast, UHF imaging enables more confident identification of subtle epileptogenic lesions, particularly in patients with drug-resistant focal epilepsy who are classified as MRI-negative on standard imaging (54, 86, 109).

Beyond initial lesion detection, 7T MRI improves delineation of lesion boundaries and surrounding cortical anatomy, which is essential for accurate integration with electrophysiological data. This improved anatomical definition supports more precise localization of the epileptogenic zone and contributes to individualized presurgical planning, including decisions regarding intracranial electrode placement and resection strategy (84, 85).

In TLE, high-resolution visualization of hippocampal subfields provides additional information on mesial temporal pathology and may help refine prognostic assessments related to postoperative seizure and cognitive outcomes (110, 111).

Neuropsychology

Neuropsychological assessment forms an essential part of the presurgical evaluation in DRE. By systematically examining cognitive domains such as memory, attention, language, and executive functioning, it helps clarify how epilepsy and its underlying pathology affect everyday cognitive abilities. These profiles offer more than a list of strengths and weaknesses; they provide a functional map of how different brain regions are contributing (or failing to contribute) to a patient's cognitive life. In this way, neuropsychology complements structural and functional imaging as well as electrophysiological data, adding a layer of interpretive depth that is often critical for understanding disease burden and planning individualized care (112, 113).

Within the presurgical work-up, cognitive patterns can help refine hypotheses about seizure lateralization, particularly in cases where MRI or EEG findings are ambiguous. In TLE, the relationship between specific cognitive functions and temporal lobe laterality is especially informative. Verbal learning, naming, and other language-mediated memory processes are most vulnerable in dominant (typically left) temporal lobe pathology, whereas visuospatial and non-verbal memory deficits more often point toward right-sided involvement (114, 115). These lateralized profiles are shaped not only by the seizure focus itself but also by disruptions in the broader neural networks that support memory, language, and executive functioning. Distinct cognitive signatures have been described across

different pathologies, for example, the pattern associated with hippocampal sclerosis differs from that seen in cortical dysplasia or extrahippocampal temporal lobe dysfunction, providing additional clues about the underlying substrate (116, 117).

Beyond localization, neuropsychology contributes meaningfully to prognostic counseling. The preoperative cognitive baseline is central to estimating the risk of postoperative decline and to identifying patients who may require early rehabilitation support. This is particularly relevant in temporal lobe surgery, where resection of mesial structures in the dominant hemisphere is associated with an increased risk of verbal memory decline, while non-dominant resections may affect visuospatial or non-verbal memory abilities (113, 118).

Recent work underscores the importance of considering structural and functional connectivity, as well as individual cognitive reserve, when predicting outcomes (117). Longitudinal follow-up remains crucial because postoperative cognitive trajectories are shaped not only by the surgery itself but also by seizure control, ASM adjustments, and neural plasticity mechanisms over time (119, 120).

Neuropsychology and hippocampal segmentation

The relationship between hippocampal structure and memory function has long been a central focus in the study of TLE. Neuropsychological assessment remains a cornerstone of clinical evaluation, particularly in the presurgical setting, where patterns of memory performance contribute to lateralization and risk estimation. In parallel, advances in neuroimaging have enabled increasingly detailed anatomical assessment of the hippocampus, prompting interest in whether structural measures at the level of hippocampal subregions may help clarify observed cognitive profiles.

The hippocampus is composed of multiple subregions with distinct cytoarchitecture and connectivity, and experimental models suggest functional specialization across subfields areas CA1, CA3, DG, and the subiculum. These distinctions have informed hypotheses linking selective subfield involvement to different aspects of memory processing, including episodic encoding, associative learning, and pattern separation (121). On this basis, several imaging studies have explored whether variation in hippocampal subfield volumes is associated with specific memory functions in both epilepsy and non-epilepsy populations (110, 122, 123).

Methodological developments have supported this line of research. Manual segmentation protocols validated against histological material, as well as atlas-based and multi-atlas approaches, have improved the anatomical delineation of hippocampal subregions (111, 124). More recently, automated and machine-learning-based methods have been introduced, aiming to increase reproducibility and facilitate application in larger cohorts (49). UHF MRI further enhances spatial

resolution and tissue contrast, offering improved visualization of internal hippocampal architecture compared with conventional field strengths (76, 111).

Despite these advances, the clinical and cognitive relevance of hippocampal subfield metrics remains an area of active investigation. Reported associations between subfield structure and memory performance vary across studies and depend on factors such as patient population, imaging methodology, cognitive task selection, and analytical approach.

From lesion detection to network pathology

Advances in UHF MRI have substantially improved the visualization of structural abnormalities in epilepsy, particularly within the temporal lobe and hippocampal formation. At 7T, subtle cortical malformations, hippocampal subfield alterations, and microstructural changes can be delineated with a level of anatomical precision that is not achievable at conventional field strengths (76, 86). These developments have strengthened the role of MRI in presurgical evaluation by increasing lesion detection rates and improving confidence in radiological interpretation.

However, improved structural resolution does not necessarily translate into improved understanding of functional outcomes. Cognitive functions such as memory depend on distributed networks involving bilateral medial temporal structures, neocortical regions, and long-range white matter connections, rather than on isolated hippocampal subregions alone (121, 125). In chronic TLE, longstanding seizures and network reorganization may further weaken the relationship between focal structural damage and cognitive performance.

Aims

The overall aim of this thesis is to evaluate the use of 7T MRI in epilepsy patients with special focus on drug-resistant cases. More specifically, the specific objectives were:

- To investigate whether the use of tensor-valued dMRI on a 7T scanner may improve MCD delineation by enabling differentiation of cortex and white matter based on a voxel´s axonal content rather than its myelin content (paper I).
- To analyse structural characteristics of malformations of cortical development at ultra-high field MRI with special focus on potential structural substrates for epileptic circuitries between deep and cortical brain lesions and a comparison to findings at lower field strength (paper II).
- To assess the potential clinical added value of 7T MRI during epilepsy surgery investigations in patients with TLE, and furthermore to assess the timing of 7T MRI use within the broader presurgical investigation process, with particular emphasis on the comparison between earlier and later stages of evaluation (paper III).
- To assess whether memory in TLE patients correlates to pathology in hippocampal subregional volumes, using a 7T scanner and automated hippocampal segmentation (paper IV).

Methods

First steps

A 7T MRI scanner (Philips Achieva 7T, Philips Healthcare, Best, the Netherlands) was installed in Lund and became operational for research on October 1, 2015. The initial phase required extensive technical calibration and protocol development to ensure stable image quality and safe operating procedures. Early efforts focused on examining healthy volunteers, which allowed optimization of acquisition parameters and familiarization with the characteristics of UHF imaging. After a prolonged period of refinement, the system reached the level of reliability necessary for research use, and examinations of study participants commenced at the end of 2016.

Patient selection

All patients included in this thesis were recruited from the Department of Neurology at Skåne University Hospital (SUS) in Lund, Sweden. Patients were enrolled between 2016 and 2021 as part of a large prospective observational study, designed to explore the clinical and scientific utility of UHF MRI in epilepsy.

All participants had a diagnosis or history of epilepsy and were referred for advanced evaluation within the regional epilepsy surgery program. The majority were followed at Skåne University Hospital, but a subset of participants was referred from other Swedish epilepsy centres and included in the cohort through national collaborations. All patients had previously undergone at least one MRI investigation at a lower-field (typically 3T) scanner before the 7T examination.

Clinical data were collected from medical records for all study participants. For patients followed at Skåne University Hospital and Linköping University Hospital, data were retrieved electronically using the local medical record system Melior and the National Patient Overview (Nationell Patientöversikt, NPÖ). For patients referred from other centres, medical records were obtained in paper form and subsequently digitised. Information on seizure history, neurophysiological investigations, imaging findings, neuropsychological assessments, and treatment outcomes were extracted and compiled into a research database.

The inclusion of patients with different epilepsy syndromes and MCD allowed for detailed sub-studies focusing on specific clinical and imaging aspects (**Table 1**). These form the basis for the studies included in this thesis.

All participants provided written informed consent prior to inclusion. The studies were approved by the Swedish Ethical Review Authority (approval numbers 2016/595, 2019/01113 and 2021/0564202).

Table 1. Overview of all studies.
MCD; malformations of cortical development, dMRI; diffusion MRI, TLE; temporal lobe epilepsy;

	Paper I	Paper II	Paper III	Paper IV
Design	Prospective imaging study	Prospective observational cohort	Retrospective clinical cohort	Prospective cross sectional
Number of participants	13	25	61	42
Epilepsy type/pathology	MCD	MCD	TLE	TLE
Clinical context	Lesion characterization	Lesion characterization and comparison between 7T and 3T	Presurgical evaluation	Cognitive assessment in TLE
Main imaging techniques	Tensor-valued dMRI	High-resolution structural MRI	High-resolution structural MRI	Automated hippocampal subfield volumes
Primary outcome	Microstructural tissue differentiation within lesions	Lesion morphology and structural connectivity	Added clinical value in presurgical workflow	Memory performance and hippocampal subfield volumes

MRI safety and contraindications

Prior to UHF MRI, all participants were screened according to established safety guidelines for 7T imaging.

Standard contraindications for MRI were applied across all studies, including non-MRI-compatible implanted medical devices, ferromagnetic implants, and other conditions deemed incompatible with UHF MRI. In addition, pregnancy was considered an exclusion criterion due to the limited safety data available for 7T MRI. Participants were also excluded if they were unable to tolerate the scanning procedure or comply with study requirements.

These safety criteria were applied consistently across all included studies, ensuring participant safety and methodological consistency throughout the thesis.

Paper I

This study included patients with radiologically confirmed MCD, that had been identified and examined with 7T MRI as a sub-group of our larger cohort. The study focused on patients whose lesions had not previously been surgically resected, to ensure that the anatomical and microstructural features of the lesions could be accurately assessed. Inclusion criteria were carefully defined to optimize data quality and reliability. Specifically, patients were required to have lesions large enough to encompass multiple voxels in the dMRI data, to allow meaningful microstructural analysis. Lesions located in areas prone to signal dropout or severe echo-planar imaging distortions were excluded, as such artefacts could compromise the interpretation of diffusion metrics. Additionally, high-resolution T1-weighted images had to be available for accurate co-registration with the dMRI data, ensuring precise anatomical localization and analysis.

Out of 34 initially eligible patients with MCD, 21 were excluded based on these criteria. Exclusion reasons included complete or partial surgical resection of the lesion (n = 3), lesions too small to be resolved in the dMRI data (n = 3), lesion locations affected by imaging artefacts (n = 6), missing or incomplete dMRI datasets (n = 8), and the absence of T1-weighted images for co-registration (n = 1). These selection criteria were applied to ensure that only patients with high-quality, analysable imaging data were included, maximizing the validity of subsequent analyses.

The final cohort consisted of 13 patients, including eight females and five males, with a mean age of 32 ± 13 years at the time of examination (**Figure 8**).

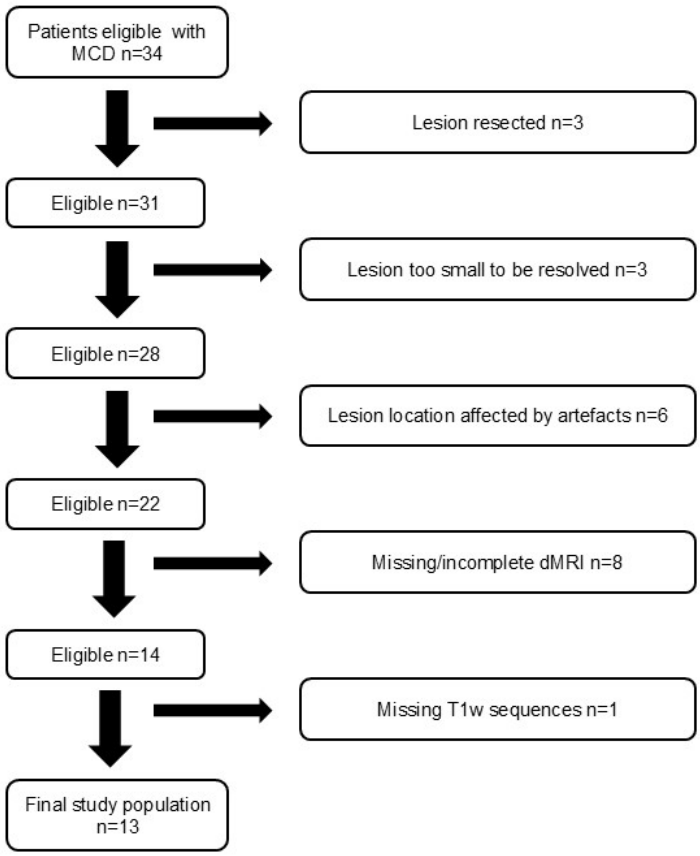

Figure 8. Flow chart describing inclusion process in paper I.

Paper II

Paper II was designed to evaluate the morphological characteristics of different MCD on 7T MRI, using previously acquired 3T MRI as the clinical reference. The study addressed whether 7T MRI provides additional or more detailed anatomical information beyond that available from conventional clinical imaging.

The study cohort consisted of the first 25 consecutive patients in whom one or more MCD lesions were identified on 7T MRI during the inclusion period. All patients had a previously known MCD lesion on clinical 3T MRI, allowing direct subject comparison across field strengths. Consecutive inclusion was applied to minimize

selection bias and to reflect a clinically relevant population referred for advanced epilepsy imaging.

Patients with prior neurosurgical intervention involving the lesion of interest were excluded, as surgical alteration could affect lesion morphology and confound interpretation of structural relationships. No additional study-specific exclusion criteria were applied.

Image analysis focused on qualitative comparison between 7T and 3T MRI. All 7T examinations were reviewed alongside the corresponding clinical MRI studies by experienced neuroradiologists with expertise in epilepsy imaging. Evaluation emphasized lesion conspicuity, delineation of lesion borders, abnormalities of cortical thickness and the gray-white matter junction, and identification of additional structural features not appreciated on conventional imaging.

Differences between 3T and 7T findings were documented and categorized according to whether 7T MRI provided new lesion detection, improved delineation of known abnormalities, or increased diagnostic confidence.

Paper III and IV

Papers III and IV are based on the same cohort of patients with (or with recent history of) drug-resistant TLE. A total of 61 (in paper III) and 63 (in paper IV), respectively, patients were initially recruited. Demographic and clinical characteristics included seizure-onset lateralization, seizure frequency, number of ASM and epilepsy duration.

All patients underwent UHF 7T MRI. Imaging protocols included high-resolution structural sequences optimized for detailed assessment of the temporal lobes and hippocampal anatomy. The acquired datasets were used both for clinical evaluation of structural abnormalities and for quantitative analysis of hippocampal volumes. Automated segmentation with ASHS was applied to derive volumetric measures for hippocampal subfields, including CA1, CA2, CA3, DG, and subiculum, as well as total hippocampal volume per hemisphere.

All patients completed a comprehensive neuropsychological assessment at their respective university hospitals as part of the presurgical work-up. The evaluations were semi-structured, ensuring that the same cognitive domains were assessed across patients, including memory, language, visuospatial abilities, attention, and executive functions. Minor variations in specific test instruments occurred across centers.

Although Papers III and IV are based on the same patient sub-cohort, they address different research questions and apply distinct analytical approaches. Paper III focused on the added clinical value of 7T MRI in the presurgical evaluation of TLE

by comparing 7T findings with prior clinical MRI and their impact on diagnostic interpretation.

For Paper IV, the shared 7T MRI and neuropsychological data were used to examine associations between memory performance and hippocampal structure. Quantitative analyses focused on total hippocampal volume and hippocampal subfield volumes derived from automated segmentation. Memory performance was summarized using composite scores for verbal and non-verbal memory based on standardized neuropsychological test results. Patients with bilateral seizure onset were excluded from lateralized analyses to ensure clear group separation.

Of the 63 initially included patients, a subset was excluded from quantitative analyses due to unsuccessful hippocampal segmentation or incomplete neuropsychological data. The final sample used for analyses in Paper IV comprised 46 patients with complete imaging and cognitive data (**Figure 9**). Paper III included all 61 patients for whom 7T and 3T/1,5T MRI were available and clinically interpretable.

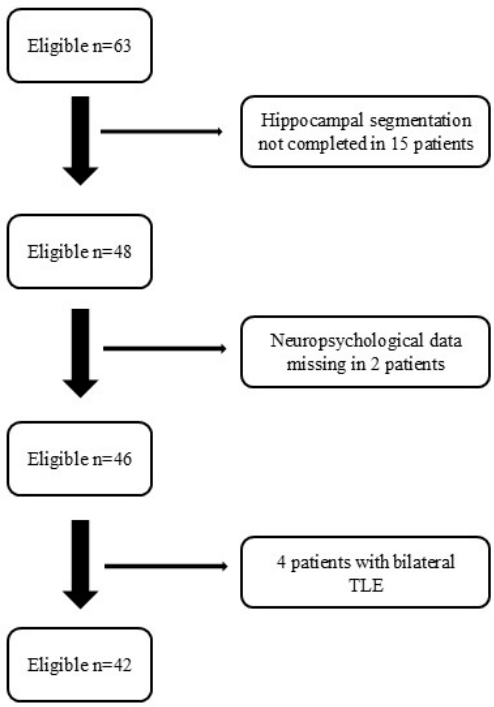

Figure 9. Flow chart describing the patient selection process in paper IV. Reproduced from Ljung et al, 2026, manuscript.

MRI acquisition and image evaluation

All participants underwent 7T MRI using a whole-body scanner (Philips Achieva, Philips Healthcare, Best, The Netherlands) equipped with a dedicated head coil. The imaging protocol included a high-resolution structural core, complemented by advanced diffusion imaging in Paper I. An overview of the sequences used across the four papers is provided in **Table 2**.

A three-dimensional (3D) T1-weighted sequence was acquired in all participants to provide high-resolution anatomical coverage of the entire brain. Submillimeter resolution was used to enable detailed visualization of cortical and mesial temporal structures.

High-resolution T2-weighted and 3D fluid-attenuated inversion recovery (FLAIR) sequences were also acquired as part of the structural protocol.

In Paper I, DWI was performed using a multi-shell acquisition with tensor-valued diffusion encoding. Both linear and spherical tensor encoding were applied, enabling estimation of conventional diffusion metrics. Diffusion data were acquired at isotropic resolution and processed using established preprocessing pipelines prior to analysis.

Papers II and III were based primarily on the structural imaging protocol. No additional research-specific sequences were acquired beyond the standard 7T structural protocol.

In Paper IV, high-resolution coronal T2-weighted images aligned perpendicular to the hippocampal long axis were acquired in addition to the whole-brain T1-weighted images. These acquisitions were specifically optimized to facilitate automated hippocampal subfield segmentation.

Image evaluation procedures differed slightly between studies. In Paper I, lesion delineation and region-of-interest definition were performed by the first author in collaboration with a senior neuroradiologist with expertise in epilepsy imaging. In Paper II, 7T images underwent an initial clinical reading, followed by a secondary expert review by a neuroradiologist with extensive experience in epilepsy imaging. In Paper III, 7T MRI examinations were evaluated as part of routine clinical practice by experienced neuroradiologists, and findings were discussed in multidisciplinary epilepsy team meetings. No additional research-specific re-reading was performed.

In Paper IV, hippocampal MRI data were visually assessed for volume reduction by two experienced neuroradiologists, and discrepancies between visual assessment and automated segmentation were further reviewed.

Table 2. Overview of 7T MRI sequences used across the four papers. MPRAGE, magnetization-prepared rapid gradient echo; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; ASHS, automated segmentation of hippocampal subfields; LTE, linear tensor encoding; STE, spherical tensor encoding.

Sequence	Resolution	Paper I	Paper II	Paper III	Paper IV
3D T1-weighted (MPRAGE)	0.6–0.7 mm isotropic	✓	✓	✓	✓
3D T2-FLAIR	0.69 x 0.69 x 1.4 mm (1.4 reconstructed to 0.7 mm)	✓	✓	✓	–
High-resolution 2D T2-weighted (coronal/axial)	0.5 × 0.5 × 0.75–1.0 mm	–	✓	✓	✓ (coronal, perpendicular to hippocampus)
DWI (tensor-valued encoding)	2.0 mm isotropic (multi-shell, LTE & STE)	✓	–	–	–
Automated hippocampal subfield segmentation (ASHS; T1+T2 input)	Based on 0.6 mm T1 + 0.5 × 0.5 × 1 mm T2	–	–	–	✓

Neuropsychological evaluation

Neuropsychological testing was performed as part of the clinical presurgical evaluation at each participating center. Verbal memory was assessed using tests such as Claeson-Dahl's Test for Verbal Learning and Memory and the Rey Auditory Verbal Learning Test (RAVLT) (126, 127). Non-verbal memory was evaluated using the Rey–Osterrieth Complex Figure Test (RCFT) and the Recognition Memory Test for Faces (Warrington) (128). Not all patients completed all memory tests due to variations in test batteries across centers.

To ensure comparability across individuals, composite scores were created for verbal and non-verbal memory. Composite scores combine related measures into domain-specific indices and are commonly used in neuropsychological research to reduce the number of statistical comparisons and improve robustness in heterogeneous clinical datasets. For verbal memory, the composite score was derived from performance on Claeson-Dahl's Test for Verbal Learning and Memory and/or the RAVLT. For non-verbal memory, the composite score was based on performance on the RCFT and/or the Warrington test. All memory scores were expressed as standard deviations from normative means.

Hippocampal segmentation

Hippocampal segmentation was performed using the ASHS framework (104, 129), an established tool for atlas-based delineation of the hippocampus and its subregions. ASHS combines high-resolution T1- and T2-weighted MRI data with a multi-atlas registration approach to generate automated segmentations of hippocampal subfields. In the present work, segmentation was based on 7T MRI, allowing improved visualization of fine anatomical details compared with conventional field strengths. The segmentation output included bilateral volumes of major hippocampal subfields, of which CA1, CA2, CA3, DG, and subiculum were selected for further analyses. All segmentations were visually reviewed to ensure anatomical plausibility and to identify potential segmentation errors, that were manually corrected- prior to quantitative evaluation.

Statistical analyses

Across the four studies, both continuous and categorical variables were analyzed. Continuous variables included diffusion-derived metrics, hippocampal volumetric measures, and neuropsychological test scores. These variables are presented as mean (SD). Categorical variables, including lesion type and classification of added clinical value, are presented as counts and percentages.

In Paper I, diffusion-derived parameters including FA, mean diffusivity (MD), and MKa were analyzed. Both voxel-wise and region-of-interest (ROI)-based approaches were used to characterize diffusion properties within lesion tissue and to compare these with normal cortex and white matter.

To evaluate how well the diffusion metrics could distinguish between cortex-like and white-matter-like tissue, receiver operating characteristic (ROC) analyses were performed. ROC curves were generated using the *perfcurve* function in MATLAB, and the area under the curve (AUC) was calculated to quantify classification performance. The emphasis was on assessing the discriminatory ability of the parameters rather than on formal hypothesis testing, reflecting the exploratory nature and limited sample size of the study.

In Paper II, descriptive statistics were used to characterise lesion types, anatomical distribution, and structural relationships identified at 7T MRI, and findings were compared qualitatively with prior clinical 3T MRI. The study was descriptive in nature and did not involve formal inferential hypothesis testing.

In Paper III, the added clinical value of 7T MRI was assessed using predefined categorical classifications. Frequencies and proportions were calculated to describe

changes in diagnostic interpretation relative to prior imaging. No additional inferential statistical testing was performed.

In Paper IV, group differences in verbal and non-verbal memory performance between patients with left- and right-sided temporal lobe epilepsy were examined using appropriate group comparison tests based on data distribution. Associations between memory performance and hippocampal structure were assessed using correlation analyses, applied separately for each hemisphere. Pearson's correlation coefficients were used for normally distributed variables, while Spearman's rank correlation coefficients were applied when distributional assumptions were not met. Analyses were performed for total hippocampal volume as well as for individual hippocampal subfields. Patients with bilateral seizure onset were excluded from lateralized analyses. Confidence intervals were reported where appropriate, and statistical significance was defined as a two-tailed p-value < 0.05.

Ethical considerations

All studies were conducted in accordance with ethical standards, receiving approval from the Swedish Ethical Review Authority. The study protocol was reviewed and approved by the relevant ethical review board (entry no. 2016/595, 2019/01113 and 2021/0564202), ensuring compliance with national regulations for human research. All data handling complied with national and institutional regulations for research involving human subjects and sensitive health information (according to general data protection regulation).

The studies involved analysis of existing clinical material and neuroimaging data from patients with focal epilepsy. Participants undergoing 7T represent a potentially vulnerable group due to both the underlying neurological condition, with the accompanied risk of having a seizure during the examination, and the specific characteristics of UHF imaging. The 7T MRI examination may induce some discomfort with anxiety or dizziness, and some participants may experience the confined environment as distressing. The examinations were performed by trained personnel with experience in 7T imaging, and participants were continuously monitored throughout the procedure, to ensure safety and well-being.

The studies involved data derived from journals as well as multi-disciplinary team conferences, which include detailed discussion.

Results

This chapter presents the principal findings from the four studies included in this thesis. The results are reported descriptively, with emphasis on imaging characteristics, lesion morphology, microstructural metrics, and clinical contributions in the presurgical evaluation of epilepsy. For clarity, each study is presented in a separate section.

Paper I

Cohort characteristics and lesion composition

Thirteen individuals with radiologically confirmed MCD met the inclusion criteria for detailed diffusion and structural imaging analysis. The cohort contained a diverse set of developmental abnormalities, comprising 25 lesions distributed across periventricular heterotopia, subcortical heterotopia, FCD, and polymicrogyria. This heterogeneity enabled systematic exploration of microstructural variation across lesion types.

Lesions varied substantially in size, depth, and anatomical relation to surrounding cortex and white matter. Many comprised multilobulated or irregular structures, particularly among the subcortical heterotopia, whereas others, especially FCD, presented as subtle cortical architectural disturbances with indistinct borders on conventional MRI.

Imaging contrasts and diffusion-derived measures

Diffusion imaging enabled calculation of FA and MKa. In reference regions, FA showed the expected higher values in white matter compared with cortex but was reduced in areas with complex fibre architecture (**Figure 10**).

In contrast, MKa demonstrated a clearer and more stable distinction between cortical and white matter regions within the predefined ROIs. Unlike FA, MKa was less influenced by fibre orientation dispersion, reflecting its orientation-independent microstructural sensitivity.

Structural T1-weighted and T2-FLAIR images showed the anticipated gray-white matter contrast in non-lesional tissue but did not provide information about underlying microstructural organization.

Lesion appearance and microstructural differentiation

On structural 7T MRI, most lesions exhibited signal characteristics similar to cortex, regardless of their anatomical depth. Internal structural heterogeneity was not clearly visible on T1-weighted or FLAIR images.

In contrast, diffusion imaging revealed microstructural variability within lesions. MKa identified regions within several lesions that displayed white-matter-like properties, particularly in deeper components adjacent to or extending toward the white matter. Superficial components more often showed cortex-like characteristics.

FA showed less differentiation within lesions, largely reflecting its sensitivity to fiber orientation rather than intrinsic microstructure (**Figure 10**).

Quantitative tissue classification

To further assess tissue characteristics, diffusion metrics were evaluated for their ability to classify tissue as cortex-like or white-matter-like. ROC analyses demonstrated that MKa provided stronger discrimination between these tissue types compared with FA.

When applied to lesion tissue, MKa identified mixed microstructural profiles in several cases, supporting the presence of both cortex-like and white-matter-like components within the same lesion. FA showed weaker discrimination and less internal differentiation.

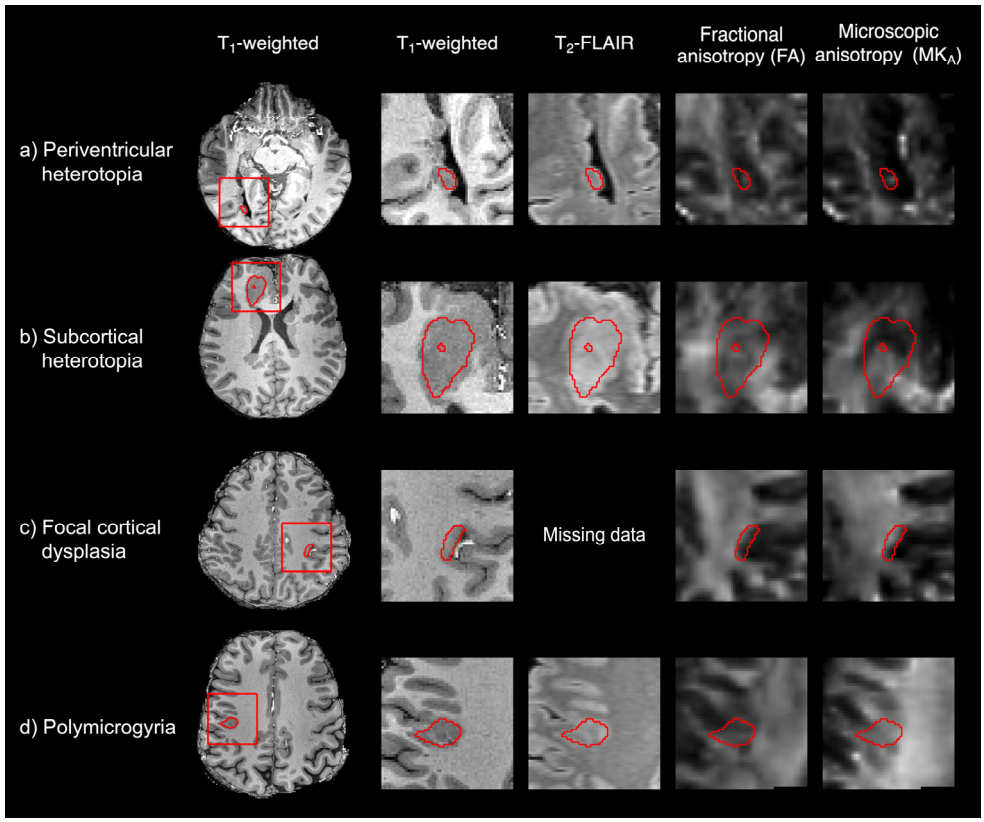

Figure 10. Imaging findings in four patients with different malformations of cortical development (MCD). For each MCD, conventional structural images (T1-weighted and T2-weighted FLAIR) and diffusion-derived maps of fractional anisotropy (FA) and microscopic anisotropy (MKa) are shown. Lesions are outlined in red.

Paper II

Cohort overview and lesion burden

The second study included the first 25 consecutive individuals in whom one or more MCD lesions were identified at 7T MRI. Across these patients, a total of 112 lesions were delineated. This unusually high lesion burden reflected the capacity of UHF imaging to visualise both overt and subtle developmental anomalies that frequently evade detection at lower field strengths.

Lesions varied substantially in morphology, hemispheric distribution, and gyral involvement. Several individuals displayed complex MCD patterns with multiple

heterotopia, combined dysplasia, or overlapping malformations within the same anatomical region.

Heterotopia morphology and signal intensity patterns

Heterotopia represented the largest lesion subgroup. PVNH showed the characteristic contiguous configuration along the ventricular walls and were consistently isointense with cortex on all conventional sequences at 7T. Subcortical heterotopia (**Figure 11)** displayed greater morphological diversity, often forming elongated or irregular clusters embedded within the white matter.

Band heterotopia presented as circumferential sheets of misplaced gray matter, with appearing patterns that were partially appreciable on high-resolution 7T sequences.

Across the cohort, heterotopia showed signal intensity similar to normal cortex. Using 7T MRI, lesion borders and internal features were more clearly defined, particularly in cases with very subtle internal structure or partial extension into adjacent white matter.

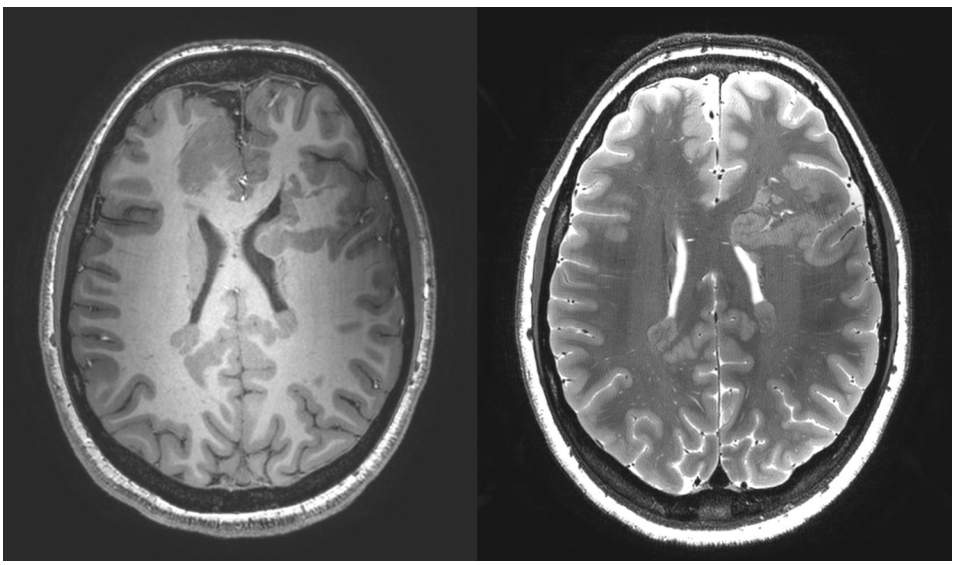

Figure 11. Axial T1-weighted (left) and T2-weighted (right) images acquired at 7T MRI demonstrate a subcortical heterotopia characterized by nodular gray matter located beneath the cortical mantle, with abnormal cortical morphology.

Structural connections between heterotopia and cortex

A central finding was the high frequency of structural associations between heterotopia and overlying cortex (**Figure 12, table 3**). These connections took several forms:

Direct tissue continuity, frequently seen between periventricular nodules and deep cortical sulci.

Gray-matter-like bridges, extending as narrow strands along presumed migrational pathways.

Vessel-associated channels, where enlarged or tortuous venous structures appeared to traverse both heterotopic and cortical compartments.

Such connections were demonstrated in nearly all patients with PVNH and in approximately half of those with subcortical heterotopia. Importantly, in regions exhibiting these connections, the corresponding cortex frequently displayed subtle architectural abnormalities consistent with FCD.

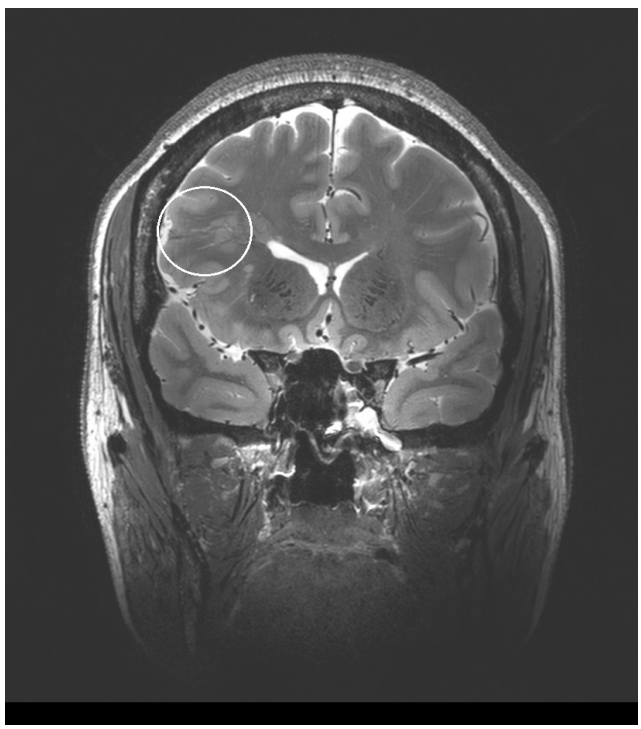

Figure 12. Coronal T2-weighted image at 7T MRI showing a connection between periventricular heterotopia and overlying cortex.

Table 3. Connections seen between grey matter heterotopia (GMH) and overlying cortex, on 7T and 3T MRI.

GMH type	Patients (n)	Lesions (n)	Heterotopia with cortical connection at 7T, n (%)	Heterotopia with cortical connection at 3T, n (%)
Periventricular nodular heterotopia	8	24 (7T) / 22 (3T)	23 (96%)	18 (82%)
Subcortical heterotopia	7	25 (7T) / 23 (3T)	13 (52%)	11 (48%)
Band heterotopia	2	8 (7T) / 8 (3T)	0 (0%)	0 (0%)

Focal cortical dysplasia: detection and characteristics

Within the cohort, 37 lesions were classified as FCD. The imaging features varied, but three patterns emerged:

- **Gray-white junction blurring**, by far the most frequent finding.
- **Cortical thickening,** variably expressed but often more conspicuous at 7T than at 3T.
- **Juxtacortical T2 or FLAIR signal changes**, including subtle transmantle features in a minority of cases.

A number of these lesions were extremely subtle and only visible at 7T MRI.

Table 4. Key imaging characteristics of focal cortical dysplasia (FCD) at 7T MRI. GM, gray matter; WM, white matter.

Feature	Findings
Patients (n)	18
FCD lesions (n)	37
Lesions per patient, median (range)	2 (1–4)
Mean lesion size, cm (range)	1.5 (0.5–5)
Predominant lobar location	Frontal > Temporal > Parietal
GM-WM junction blurring	30 lesions (81%)
Cortical thickening	11 lesions (30%)
Cortical signal intensity changes	18 lesions (49%)
Juxtacortical white matter signal changes	18 lesions (49%)
Transmantle white matter signal changes	11 lesions (30%)
Lesions with subtle imaging features	43%

Comparison with clinical 3T MRI

Retrospective review of prior 3T MRI showed a marked discrepancy in lesion detection. While GMH were typically visible at 3T, their internal architecture and connectivity to cortex were seldom appreciated. In contrast, a substantial number of dysplastic lesions were either missed or mischaracterised in the original clinical reports. Upon re-evaluation with knowledge of the 7T findings, roughly half of the previously unreported FCD could be retrospectively identified, though often with limited confidence.

Table 5. Comparison between different malformations of cortical development (MCD) seen on 7T and 3T MRI. FCD, focal cortical dysplasia; GMH, grey matter heterotopia.

MCD	7T, n	3T second reading, n (%)	Original 3T, n (%)
FCD	37	21 (57%)	11 (30%)
GMH	57	53 (93%)*	57 (100%)
Other MCD	18	18 (100%)	15 (83%)

*Four lesions in one patient with 3T images could not be retrieved for second reading.

Paper III

Cohort and evaluation context

Sixty-one individuals with drug-resistant TLE underwent 7T MRI as part of their presurgical evaluation. Most patients (n = 54) had previously been examined with a dedicated 3T epilepsy MRI protocol. In addition, three patients had undergone MRI according to an epilepsy surgery protocol at 1.5T, and four patients had been examined at 3T without an epilepsy-specific acquisition protocol.

The cohort included a broad range of clinical presentations, encompassing classical mesial TLE, suspected dual pathology, patients previously classified as MRI-negative, and individuals with unclear seizure lateralisation following non-invasive investigations.

Added value in the presurgical workflow

7T MRI contributed meaningful value in slightly more than half of the patients (n=31). Added value was defined in four categories:

1. Clarification of equivocal findings from 3T MRI (added value score: A)

In 12 patients 7T MRI provided clarification of abnormalities that had been noted but remained equivocal on prior 3T imaging. Findings such as hippocampal disruption of internal structures, subtle blurring of the gray-white matter junction, or small subcortical signal changes could be more confidently interpreted at UHF strength.

2. Exclusion of pathology suspected at lower field strength (added value score: B)

In some individuals, abnormalities suspected on prior MRI examinations could not be confirmed at 7T. Irregularities seen at lower field strength, particularly in regions prone to partial-volume effects such as the hippocampus or temporal pole, were reclassified as normal anatomical variation or imaging artefacts.

3. Detection of new structural abnormalities (added value score: C)

In likewise high number of patients (n= 12), 7T MRI revealed structural abnormalities that had not been detected on earlier imaging. These newly identified findings included subtle FCD, fine hippocampal structural alterations with atrophy and signal increase, and focal vascular or cavitary changes located at or near the gray-white matter interface.

4. Patients without additional at 7T MRI (added value score: 0)

In approximately half of the cohort, 7T MRI did not provide additional structural information compared with prior imaging. In these patients, the findings observed at 7T were concordant with those identified on previous MRI examinations, including both cases with visible structural abnormalities and cases without detectable lesions.

In patients with previously identified abnormalities, 7T MRI confirmed the presence, location, and overall appearance of the lesion without further refinement of lesion boundaries or internal structure. In patients without detectable abnormalities on prior MRI, 7T MRI did not reveal structural pathology. Consequently, the presurgical assessment in these cases remained unchanged with respect to imaging findings.

Table 6. Added value of 7T MRI. Added value scored as 0, A, B or C (0=no added value; 0=no added value, A=lesion confirmation, B=lesion exclusion, C=increased hit rate).

Phase of presurgical investigation	Patients examined with 7T MRI (n)	Cases with added clinical value (n, %)	Added value category (0 / A / B / C)
Phase 1: Initial non-invasive evaluation	28	14 (50%)	0:14 A:6 B:3 C:5
Phase 2: Advanced non-invasive investigations	14	6 (43%)	0:8 A:3 B:2 C:1
Phase 3: Invasive EEG planning	19	11 (58%)	0:8 A:3 B:3 C:5
Total cohort	61	31 patients	

Additional observations of mesial temporal anatomy

A limited number of patients demonstrated hippocampal malrotation (HIMAL). While HIMAL was considered an anatomical variant and classified as MRI-negative when occurring in isolation, 7T MRI provided additional detail in two patients where features consistent with HS were visualized at 7T but were not evident on prior 3T imaging.

Paper IV

Cohort characteristics

Of the 63 patients initially included, a number were excluded due to unsuccessful hippocampal segmentation or incomplete neuropsychological data. Automated hippocampal segmentation could not be completed for 13 patients, and in two additional patients, segmentation was only successful for one hemisphere. Neuropsychological data were missing for two patients. The final dataset therefore comprised 46 patients with complete imaging and cognitive data. Four of these patients were excluded from lateralized analyses because of bilateral seizure onset. The remaining cohort consisted of 29 patients with left TLE and 13 patients with right TLE (**Figure 9**).

The time interval between the neuropsychological assessment and the 7T MRI examination varied across patients. The two assessments could be performed on the same day or separated by several years, with a maximum interval of just under six years.

Memory Performance by Seizure Lateralisation

Two composite scores were generated to represent verbal and non-verbal memory performance (**Table 8**). Across the cohort, mean verbal memory z-scores were -0.6 (95% CI -1.1 to -0.1) in patients with left TLE and -0.1 (95% CI -0.1 to -0.05) in patients with right TLE**.** For non-verbal memory, mean z-scores were -1.0 (95% CI -1.5 to -0.5) in left TLE and -1.3 (95% CI -1.9 to -0.7) in right TLE.

Although the direction of differences followed the expected material-specific pattern, group comparisons did not demonstrate statistically significant differences between left- and right-sided TLE.

Hippocampal Volumes and Memory Performance

Associations between memory composite scores and total hippocampal volumes are presented in **Table 7**.

In patients with left-sided TLE, verbal memory showed a statistically significant negative correlation with right hippocampal volume. No other correlations reached statistical significance.

In patients with right-sided TLE, correlations between memory performance and total hippocampal volumes were moderate in magnitude but did not reach statistical significance.

Table 7. Associations between total hippocampal volume and memory composite scores (Spearman´s ρ, 95% confidence interval. TLE, temporal lobe epilepsy.

Hippocampal volume	Memory composite score	Left TLE (n=29)	Right TLE (n=13)
Left hippocampus	Verbal memory	−0.15 (−0.51 to 0.36)	−0.56 (−0.85 to 0.13)
	Non-verbal memory	−0.09 (−0.42 to 0.32)	0.09 (−0.58 to 0.67)
Right hippocampus	Verbal memory	−0.46 (−0.70 to −0.03)	−0.40 (−0.76 to 0.04)
	Non-verbal memory	0.04 (−0.38 to 0.45)	0.23 (−0.46 to 0.75)

Hippocampal Subfield Volumes and Memory Outcomes

Subfield-specific analyses revealed predominantly weak associations (**Table 8**). In patients with left-sided TLE (n = 29), correlations between verbal memory and subfield volumes were generally weak. The strongest associations were observed in the right hemisphere, where CA1 (r = -0.39) and dentate gyrus (r = -0.40) showed moderate negative correlations with verbal memory. All remaining correlations ranged approximately between -0.30 and 0.30. Associations between subfield volumes and non-verbal memory were similarly weak across both hemispheres.

In patients with right-sided TLE (n = 13), correlations were more variable. The strongest associations with verbal memory were observed for right CA2 (r = -0.64) and left CA1 (r = -0.60). Several additional subfields showed moderate negative correlations with verbal memory (approximately -0.29 to -0.48). In contrast, correlations with visual memory were small and inconsistent, generally ranging between -0.14 and 0.34.

Table 8. Volumes of hippocampal substrates and memory functions.TLE; temporal lobe epilepsy, HC; hippocampal, MTL; mesial temporal lobe, CA; cornu ammonis, DG; dentate gyrus, Sub; subiculum.

Left TLE Verbal memory: -0.6 (95% CI: -1.1 – (-0.1)) Non-verbal memory: -1.0 (95% CI: -1.5– (-0.5))										
	HC structures volume, left MTL [mm^3]					HC structures volume, right MTL [mm^3]				
	CA1	CA2	CA3	DG	Sub	CA1	CA2	CA3	DG	Sub
Mean (n=29)	651.3	26.2	168.0	478.7	991.7	763.9	64.5	139.1	526.4	1,141.4
95% CI	595.3–707.2	21.9–30.4	150.1–185.8	439.2–518.2	939.0–1,044.4	699.1–828.7	59.4–69.7	126.0–152.1	499.4–553.4	1,083.2–1,199.7
Pearson's ρ vs. verbal memory	-0.24	-0.12	0.10	0.03	-0.16	-0.39	0.23	-0.16	-0.40	-0.23
Pearson's ρ vs. non-verbal memory	-0.30	0.00	0.04	0.03	-0.19	0.06	0.07	0.04	-0.14	-0.07
Right TLE Verbal memory: -0.1 (95% CI: -0.1– (-0.05)) Non-verbal memory: -1.3 (95% CI: -1.9– (-0.7))										
	HC structures volume, left MTL [mm^3]					HC structures volume, right MTL [mm^3]				
	CA1	CA2	CA3	DG	Sub	CA1	CA2	CA3	DG	Sub
Mean (n=13)	694.3	32.3	160.2	498.2	989.0	745.9	59.5	149.4	552.5	1085.4
95% CI	640.2–748.5	26.1–38.5	140.1–180.3	467.5–528.8	921.9–1,056.0	613.8–878.0	44.6–74.4	122.7–176.0	466.2–638.8	984.8–1,185.9
Pearson's ρ vs. verbal memory	-0.6	-0.2	-0.2	-0.2	-0.5	-0.3	-0.6	-0.4	-0.3	-0.3
Pearson's ρ vs. non-verbal memory	0.0	0.2	0.1	0.1	0.1	0.3	0.1	-0.1	0.1	0.3

Discussion

Main findings

This thesis explored the role of UHF 7T MRI in the evaluation of focal epilepsy from different perspectives, including lesion detection, structural characterization, and the relationship between brain morphology and cognitive function. Across the included studies, 7T MRI consistently improved the visualization and delineation of epilepsy-related structural abnormalities. At the same time, the findings demonstrate that increased anatomical precision does not necessarily translate into improved prediction of functional or cognitive outcomes.

Papers I and II showed that 7T MRI enables detection and detailed characterization of subtle malformations of cortical development, including structural relationships between heterotopia and adjacent cortex that are difficult to appreciate at lower field strengths. Paper III further demonstrated that these imaging advantages may have direct clinical relevance by increasing diagnostic confidence and, in selected cases, influencing presurgical evaluation. In contrast, Paper IV showed that detailed volumetric assessment of hippocampal subfields did not yield robust or consistent associations with memory performance. Overall, the studies illustrate both the strengths and the limitations of UHF MRI: while it markedly enhances structural assessment, its ability to predict cognitive function based on volumetry alone appears limited.

7T MRI in the Evaluation of Focal Epilepsy

UHF MRI has emerged as an important tool for improving the detection and characterization of epileptogenic lesions. In Papers I–III, the increased spatial resolution and contrast at 7T facilitated visualization of subtle cortical abnormalities, improved delineation of lesion borders, and revealed microstructural features not visible at conventional field strengths. These advantages were evident in both patients with MCD and previously MRI-negative epilepsy.

Paper II extended this perspective by demonstrating structural association between heterotopia and overlying cortex, supporting the concept that MCD may involve distributed structural networks rather than isolated nodules. This observation aligns

with definition of epilepsy as a network disorder and provides a morphological substrate for electrophysiological and clinical findings reported in previous literature (13, 18).

In Paper III, the added value of 7T MRI was assessed in a clinical context. While not all examinations resulted in new diagnostic findings, 7T MRI contributed to improved lesion characterization and, in some cases, altered clinical interpretation. These findings support the use of UHF MRI as a complementary imaging modality in selected patients undergoing presurgical evaluation, particularly when conventional imaging is inconclusive.

The risk of overinterpretation at UHF

While UHF MRI offers clear advantages in lesion detection and anatomical detail, it also raises an important question: can the increased resolution lead to overinterpretation? As spatial resolution and contrast improve, subtle structural variations that were previously invisible become detectable. However, not all visible irregularities represent clinically relevant pathology.

At 7T, normal anatomical variability, minor cortical irregularities, or field strength-specific artefacts may appear more conspicuous than at lower field strengths. This may increase the risk of attributing epileptogenic significance to findings that are incidental or unrelated to seizure generation. Most probably a higher image detail does not necessarily equate to higher diagnostic certainty.

The distinction between true pathological abnormalities and benign structural variation becomes particularly challenging in patients with subtle malformations or in those previously classified as MRI-negative. The temptation to identify a structural correlate for seizures may be stronger when highly detailed images are available. However, without concordance from semiology, electrophysiology, and other modalities, structural findings alone should be interpreted with caution.

This consideration reinforces the importance of multidisciplinary evaluation. UHF MRI should not be viewed as a definitive arbiter of pathology, but as one component within a broader clinical framework. Increased visibility must be balanced with critical interpretation to avoid both under- and overdiagnosis. In this sense, technical progress demands parallel development of interpretative rigor and clinical restraint.

Structural precision versus functional relevance

One of the themes emerging from this thesis is the distinction between improved structural precision and functional relevance. While Papers I–III demonstrate that 7T MRI refines anatomical assessment, Paper IV highlights the limitations of structural imaging when used to predict cognitive outcomes. Despite detailed segmentation of hippocampal subfields, associations between volumetric measures and memory performance were weak, inconsistent, and often counterintuitive.

These findings suggest that volumetry, even at UHF strength, captures only a limited aspect of the neural substrates underlying cognition. Cognitive functions such as memory depend on distributed networks involving bilateral medial temporal structures, neocortical regions, and long-range connections. In chronic TLE, additional factors such as functional reorganization, compensatory recruitment, and disease duration further complicate structure-function relationships (121, 125).

From this perspective, the lack of strong correlations in Paper IV should not be interpreted as a failure of 7T MRI, but rather as an indication that increasing spatial resolution alone is insufficient to explain complex cognitive outcomes. Instead, the results emphasize the need to move beyond isolated structural markers toward integrated models of brain function.

Limitations and Methodological Considerations

Several methodological factors should be considered when interpreting the findings of this thesis, particularly in light of the evolving clinical and technical implementation of UHF MRI. Data collection for the included studies spans a period during which 7T MRI was newly introduced into clinical and research use. During the early phase of this period, acquisition protocols, hardware performance, and image reconstruction techniques were still undergoing optimization. Subsequent upgrades of the scanner's hardware and software, as well as refinements in sequence design, led to gradual improvements in image quality over time.

In parallel with these technical developments, there was a substantial learning curve in the clinical interpretation of UHF MRI. Radiologists and clinicians gained experience in distinguishing pathological findings from field strength-specific artefacts, normal anatomical variants, and previously unseen microstructural features. Early examinations may therefore have been interpreted more conservatively, whereas later studies benefited from increased familiarity with 7T-specific image characteristics and greater confidence in lesion identification and characterization. This evolving expertise likely contributed to variability in image evaluation across the study period.

Additional methodological considerations include heterogeneity in patient characteristics and clinical work-up, reflecting the real-world setting of tertiary epilepsy care. Neuropsychological assessments were performed as part of routine presurgical evaluation across multiple centers, necessitating the use of composite scores to ensure comparability. While this approach improves robustness and reduces multiple testing, it may obscure more specific cognitive processes captured by individual tests (120, 130).

Finally, variability in the timing between MRI acquisition and neuropsychological assessment represents an inherent limitation. Given the chronic and dynamic nature of epilepsy, changes in seizure burden, medication, and network reorganization over time may further weaken direct associations between structural measures and cognitive performance.

All these methodological factors highlight the challenges of conducting research during a period of rapid technological and clinical development. They also emphasize that the findings of this thesis should be interpreted within the context of an evolving imaging modality, where both technical performance and clinical expertise improved over time.

Methodological considerations in 7T hippocampal segmentation

Automated segmentation of hippocampal subfields at UHF MRI offers the possibility of detailed volumetric assessment of small and anatomically complex structures. However, segmentation at 7T is not without methodological challenges. Increased susceptibility effects, signal inhomogeneities, and partial volume effects may influence segmentation accuracy, particularly in patients with pronounced pathology or anatomical distortion (107, 111).

Atlas-based segmentation methods are dependent on the anatomical assumptions embedded in the reference atlas. These assumptions may not fully capture inter-individual variability or structural alterations related to chronic epilepsy. In the present cohort, segmentation failures and unilateral segmentation in a subset of patients likely reflect such technical and anatomical constraints. These factors should be considered when interpreting the absence of strong structure-function associations, as measurement variability may attenuate subtle volumetric effects.

MRI-negative epilepsy; clinical reality and research challenges

MRI-negative epilepsy remains one of the most challenging situations in presurgical evaluation. The absence of a visible lesion is not only a diagnostic difficulty; it has clear consequences for outcome. Surgical results are consistently lower in MRI-negative patients (40, 58). In everyday clinical work, these numbers are not abstract statistics - they directly affect how confidently we can counsel patients.

At the same time, the term “MRI-negative” deserves reflection. It does not necessarily mean that there is no structural abnormality. Rather, it often means that the abnormality is below the detection threshold of the imaging technique used at that time. As imaging evolves, some patients who were previously considered MRI-negative are reclassified as lesional. This raises an important question, whether we are truly dealing with different biological entities, or with different levels of visibility.

Improved imaging, including UHF MRI, may reduce the number of patients categorized as MRI-negative. However, better visualization does not automatically translate into better outcomes. Even when subtle abnormalities are detected, it remains difficult to determine whether they fully explain the seizure network. In MRI-negative cases, the epileptogenic process may be more diffuse, less anatomically confined, or more network-based.

From a research perspective, MRI-negative epilepsy also illustrates the practical difficulties of studying rare and highly selected patient groups. In a small country as Sweden, the absolute number of surgical candidates is limited. Within that population, MRI-negative patients represent only a fraction. Recruiting large, homogeneous cohorts is therefore challenging. This affects statistical power and limits the possibility of detailed subgroup analyses.

Another challenge is the rapid development of imaging technology. Data collection for advanced MRI studies often spans several years. During that time, scanners are upgraded, sequences are optimized, and interpretative experience improves. The field evolves while data are being collected, and as a result, studies inevitably represent a moving target rather than a fixed technological method.

These realities require certain consideration. Imaging plays a central role in presurgical evaluation, but it cannot replace clinical judgment or multimodal integration.

Epilepsy Surgery and Clinical Decision Making

For patients with DRE, surgery remains the most effective treatment option, with long-term seizure freedom rates exceeding 60–70% when a resectable lesion is identified (34, 40). Imaging therefore plays a crucial role in defining surgical candidacy. The transition from 3T to 7T MRI deepens this process by providing previously unavailable structural information that may influence whether a patient proceeds to invasive EEG monitoring, whether implantation plans need to be adjusted, and how resection boundaries are defined.

In the present cohort, the added value of 7T MRI was evident in more than half of the patients. In some cases, subtle hippocampal abnormalities became clearer; in others, cortical lesions were newly detected, or previously suspected abnormalities could be confidently dismissed. Similar clinical effects have been described in other 7T epilepsy populations (131, 132).

This is particularly relevant for planning stereo-EEG, during which a precise anatomical hypothesis guides electrode placing. Even small lesions identified at 7T may refine the presumed epileptogenic zone and help avoid non-targeted sampling. While the surgical impact of 7T MRI continues to evolve, our experience indicates that UHF MRI has already begun to influence clinical dialogue and multidisciplinary decision-making in complex epilepsy cases.

Importantly though, clinical decision-making in epilepsy surgery is never based on a single investigation. Surgical candidacy and strategy are determined through an integrated assessment that combines seizure semiology, electrophysiological data, structural and functional imaging, and neuropsychological evaluation, where concordance of the findings lead to further discussions. Within this context, the findings from Paper IV should be interpreted with nuance. Although hippocampal subfield volumes did not show robust associations with memory performance at the group level, this does not preclude potential clinical relevance in individual cases. Hippocampal segmentation may be therefore regarded as a complementary tool that enhances anatomical understanding, rather than as a standalone determinant of cognitive outcome.

When should 7T MRI be implemented in clinical practice?

As UHF MRI becomes more accessible, an important question is when it should be used in routine care. The advantages of 7T are clear from a technical perspective, but clinical implementation should be selective and guided by patient need.

At present, 7T MRI appears most relevant in complex presurgical cases, particularly when conventional imaging is inconclusive or when a suspected lesion is subtle. In such situations, additional structural details may help refine the anatomical hypothesis and support clinical decision-making (54, 86). In contrast, in patients with a clearly defined lesion on 3T MRI and concordant clinical findings, the additional value of 7T may be limited.

Implementation also depends on experience and infrastructure. Interpretation of 7T images requires familiarity with field-specific artefacts and normal anatomical variation (76). Without sufficient expertise, increased image detail does not automatically improve diagnostic accuracy. For this reason, 7T MRI is likely best integrated within specialized epilepsy centers where imaging findings can be interpreted in a multidisciplinary context.

Rather than replacing conventional MRI, 7T should be regarded as an additional tool that can be deployed when standard evaluation leaves uncertainty. As further outcome data become available, its role may expand, but careful patient selection will remain essential to ensure that technological advances translate into meaningful clinical benefit.

Working within an evolving clinical and technological landscape

This thesis was conducted during a long period when 7T MRI gradually transitioned from a research tool toward a more clinically integrated modality. Imaging protocols evolved, clinical experience increased, and interpretative frameworks shifted over time. This dynamic context creates both opportunity and complexity. Patients benefit from continuous technical improvement, but at the same time a balance is needed to overcome all the challenges.

Conclusions and future perspectives

This thesis demonstrates that UHF 7T MRI provides clear advantages for the structural evaluation of focal epilepsy. Across the included studies, 7T MRI improved the detection and delineation of subtle epileptogenic lesions, particularly in patients with MCD or previously inconclusive conventional imaging. These strengths support the role of 7T MRI as a valuable complementary tool in the presurgical assessment of selected patients.

At the same time, the findings show that increased anatomical detail does not automatically translate into improved prediction of clinical or cognitive outcomes. In particular, the results from Paper IV indicate that detailed volumetric measures of hippocampal subfields, even when derived from UHF imaging, have limited value when used in isolation to estimate memory performance. This highlights an important clinical reality: cognitive outcome in epilepsy surgery reflects distributed network function and long-standing disease effects rather than focal structural measures alone.

From a clinical perspective, these results reinforce the importance of multidisciplinary decision-making in epilepsy surgery. High-resolution imaging should be interpreted alongside seizure semiology, electrophysiological data, and neuropsychological assessment, rather than as a standalone determinant of surgical risk or benefit. We claim that 7T MRI contributes by improving anatomical confidence and hypothesis generation but does not replace established evaluation strategies.

Looking forward, future research and clinical development should focus less on identifying single imaging biomarkers and more on combining complementary sources of information. Multimodal approaches that will integrate structural and functional imaging, and cognitive assessment are likely to provide a more realistic reflection of the mechanisms underlying seizure generation and cognitive outcome. Prospective studies embedded in clinical workflows, where imaging and cognitive testing are performed within the same time frame, may further strengthen relevance.

In conclusion, UHF MRI represents a meaningful advance in epilepsy imaging, particularly for lesion detection and anatomical understanding. Its greatest clinical value lies in supporting, rather than replacing, multidisciplinary evaluation and individualized clinical judgement. By situating advanced imaging within real-world decision-making, future work may continue to refine the role of 7T MRI in epilepsy surgery while maintaining a patient-centered perspective.

Populärvetenskaplig sammanfattning

Epilepsi är en vanlig neurologisk sjukdom som drabbar miljontals människor världen över. För de flesta kan anfallen kontrolleras med läkemedel, men hos ungefär en tredjedel kvarstår anfallen trots korrekt behandling. Denna form kallas läkemedelsresistent epilepsi och kan ha stor påverkan på livskvalitet, kognition och psykisk hälsa. För många av dessa patienter kan epilepsikirurgi vara ett effektivt behandlingsalternativ, förutsatt att man kan identifiera den del av hjärnan där anfallen uppstår.

Magnetkameraundersökning (MRI) spelar en avgörande roll i utredningen inför epilepsikirurgi. Med hjälp av MRI kan strukturella förändringar i hjärnan, såsom ärrbildning eller medfödda utvecklingsavvikelser, identifieras. Samtidigt är det välkänt att vissa epileptiska förändringar är mycket subtila och ibland inte syns på traditionell MRI med lägre magnetfält. Detta innebär att vissa patienter klassificeras som ”MRI-negativa”, trots att det finns en underliggande strukturell orsak till epilepsin.

I denna avhandling undersöks hur ultrahögfälts-MRI vid 7 Tesla (T) kan förbättra möjligheten att upptäcka och karakterisera epilepsirelaterade hjärnförändringar. Jämfört med konventionell MRI ger 7T MRI högre detaljrikedom och bättre kontrast, vilket gör det möjligt att visualisera finare strukturer i hjärnan. Studierna i avhandlingen visar att 7T MRI kan avslöja förändringar som tidigare varit svåra eller omöjliga att se, särskilt vid missbildningar i hjärnbarken och vid epilepsi som utgår från tinningloben.

Utöver strukturell avbildning har avhandlingen även använt avancerade diffusionsmetoder för att studera hjärnans mikrostruktur. Dessa metoder ger information om hur nervceller och nervbanor är organiserade på mikroskopisk nivå och kan visa förändringar även när hjärnan ser normal ut på vanlig MRI. Resultaten tyder på att epilepsi ofta påverkar hjärnan mer utbrett än den synliga lesionen ensam, vilket stödjer en syn på epilepsi som en nätverkssjukdom.

Avhandlingen belyser också sambandet mellan hjärnans struktur och kognitiva funktioner, särskilt minne. Genom att analysera olika delar av hippocampus - en hjärnstruktur som är central för minnesfunktion - undersöks hur strukturella förändringar relaterar till minnesprestation hos patienter med temporallobsepilepsi. Resultaten visar att sambandet mellan hippocampus volym och minne är komplext

och inte alltid linjärt, vilket understryker vikten av att kombinera bilddiagnostik med neuropsykologisk utvärdering.

Sammanfattningsvis visar denna avhandling att 7T MRI kan ge värdefull tilläggsinformation vid utredning av läkemedelsresistent epilepsi. Genom att förbättra möjligheten att identifiera subtila hjärnförändringar och förstå deras relation till både epileptiska anfall och kognitiv funktion, kan 7T MRI bidra till mer träffsäkra diagnoser och bättre underlag för individualiserad behandling och kirurgisk planering i framtiden.

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