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Improving patient selection by investigation of methods used for predicting verbal memory following surgery.

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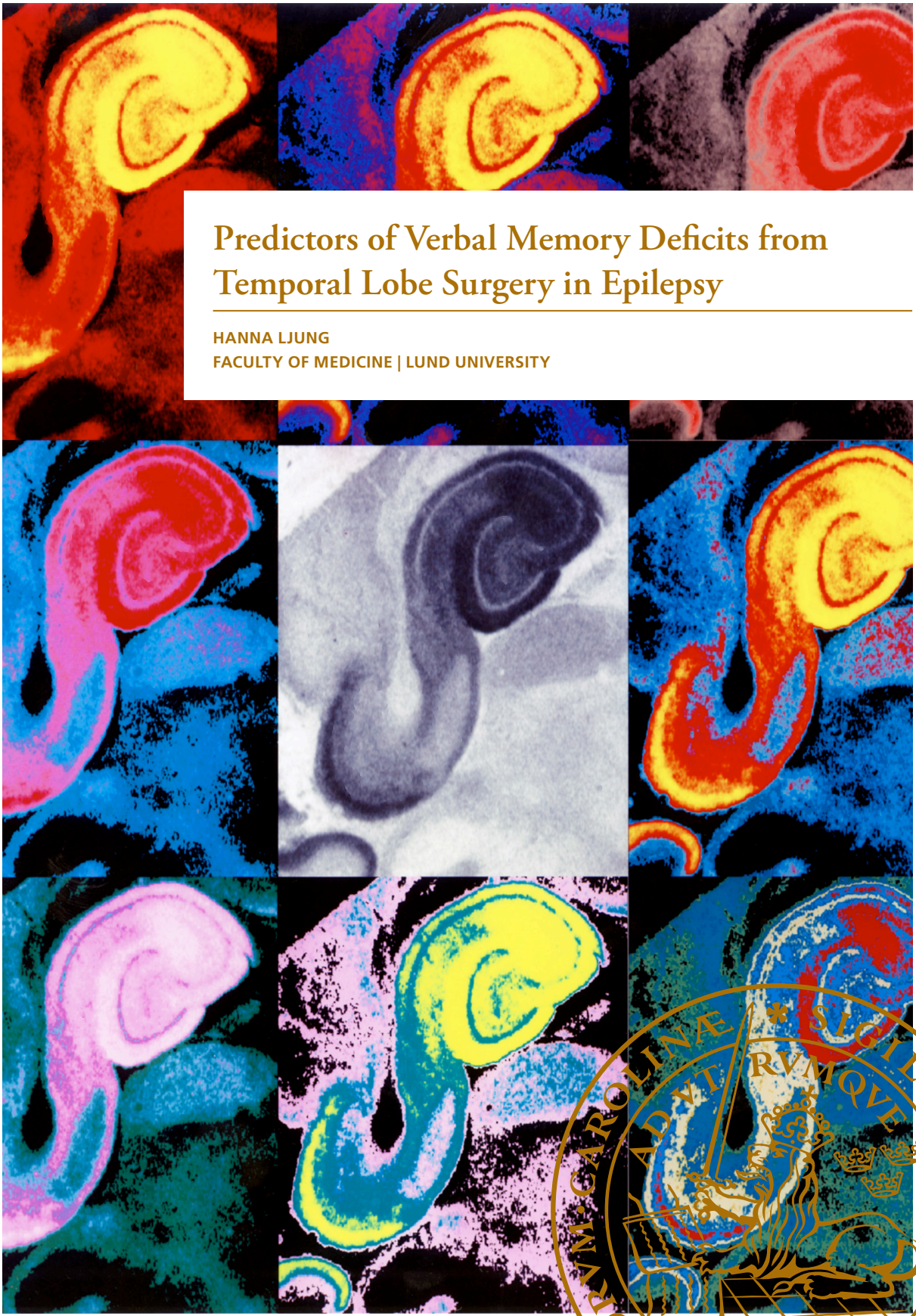

Predictors of Verbal Memory Deficits from Temporal Lobe Surgery in Epilepsy

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FACULTY OF MEDICINE | LUND UNIVERSITY

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LUND
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Abstract

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All patients in the thesis either had a pharmaco-resistant or difficult-to-treat temporal lobe epilepsy (TLE), or had received TLR. In paper 1, functional magnetic resonance imaging (fMRI) memory paradigm, consisting of a verbal memory task and a non-verbal memory task, was used to predict post-surgical verbal memory deficits prior to TLR. In paper 2, a neuropsychological follow-up of patients that had received longitudinal hippocampal depth electrodes during work-up for TLR was carried out to determine if such electrodes entail a risk for verbal memory deterioration. Paper 3 used structural 7 Tesla MRI to investigate how hippocampal subregions, and visual inspection of the hippocampus, correlate with memory performance in patients with TLE. In paper 4, the coherence between two common memory tests used for assessing verbal memory prior to TLR was evaluated.

The fMRI memory paradigm did not suffice as an additional indicator for verbal memory deterioration from TLR, while language activation detected by fMRI during verbal encoding did. Neuropsychological long-term follow-up revealed a risk of verbal memory deterioration from longitudinal hippocampal depth electrodes in the left hippocampus. Correlations were found between volumes of left hippocampal subregions and both verbal and non-verbal memory variables. Visual MRI inspection suggested modest correlation between both left and right hippocampal pathology, and verbal and non-verbal memory. The construct structure of the two verbal memory tests showed no coherence for testing verbal recall, and one of the tests correlated significantly with non-verbal memory.

The results indicate that (1) fMRI language detection might foresee post-surgical verbal memory loss, (2) longitudinal hippocampal depth electrodes may harm verbal memory, (3) hippocampal subregion volumetry detects subregion-specific memory deficits and (4) verbal memory tests may be contaminated by non-verbal memory while others may not, rendering them non-interchangeable. All studies in this thesis provided information that should be considered, and may improve, pre-surgical assessment in TLR.

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Table of Contents

Abstract

Aim: The most common surgical treatment of epilepsy is temporal lobe resection (TLR). The aim of this thesis was to evaluate the tools used in pre-surgical work-up for TLR to predict post-surgical memory outcome and to improve selection of patients eligible for TLR.

Methods: All patients in the thesis either had a pharmaco-resistant or difficult-to-treat temporal lobe epilepsy (TLE), or had received TLR. In paper 1, functional magnetic resonance imaging (fMRI) memory paradigm, consisting of a verbal memory task and a non-verbal memory task, was used to predict post-surgical verbal memory deficits prior to TLR. In paper 2, a neuropsychological follow-up of patients that had received longitudinal hippocampal depth electrodes during work-up for TLR was carried out to determine if such electrodes entail a risk for verbal memory deterioration. Paper 3 used structural 7 Tesla MRI to investigate how hippocampal subregions, and visual inspection of the hippocampus, correlate with memory performance in patients with TLE. In paper 4, the coherence between two common memory tests used for assessing verbal memory prior to TLR was evaluated.

Results: The fMRI memory paradigm did not suffice as an additional indicator for verbal memory deterioration from TLR, while language activation detected by fMRI during verbal encoding did. Neuropsychological long-term follow-up revealed a risk of verbal memory deterioration from longitudinal hippocampal depth electrodes in the left hippocampus. Correlations were found between volumes of left hippocampal subregions and both verbal and non-verbal memory variables. Visual MRI inspection suggested modest correlation between both left and right hippocampal pathology, and verbal and non-verbal memory. The construct structure of the two verbal memory tests showed no coherence for testing verbal recall, and one of the tests correlated significantly with non-verbal memory.

Conclusions: The results indicate that (1) fMRI language detection might foresee post-surgical verbal memory loss, (2) longitudinal hippocampal depth electrodes may harm verbal memory, (3) hippocampal subregion volumetry detects subregion-specific memory deficits and (4) verbal memory tests may be contaminated by non-verbal memory while others may not, rendering them non-interchangeable. All studies in this thesis provided information that should be considered, and may improve, pre-surgical assessment in TLR.

Sammanfattning på svenska

Epilepsi är en av de vanligaste kroniska neurologiska sjukdomarna och omkring 0,7 % av befolkningen har en aktiv epilepsi. Epilepsi försämrar självupplevd livskvalitet, ökar risken för socialt stigma och psykisk sjukdom, kan påverka minne och kan leda till för tidig död. Ungefär en tredjedel av de som har epilepsi blir inte anfallsfria med hjälp av mediciner och dessa brukar definieras som terapirefraktära. För en del av de terapirefraktära patienterna är epilepsioperation en möjlighet till att uppnå anfallsfrihet. Ungefär 60 - 70% av de som opereras är anfallsfria även efter 10 år. De flesta epilepsioperationer som utförs på vuxna görs för att behandla temporallobsepilepsi (TLE), där de epileptiska anfallen har sitt ursprung i den del av hjärnan som kallas för tinningloben (= temporalloben). Därför kallas denna typ av operation för temporallobsresektion (TLR) och innebär att en del av temporalloben skärs bort.

Epilepsioperation innebär risker. En av riskerna vid TLR är att patienterna får en minnesförsämring av operationen. Patienter med TLE har ofta anfall som startar i hippocampus, som är en struktur i mittersta delen av temporalloben. Hippocampus har en avgörande roll för minnet, vänster hippocampus för verbalt minne och höger hippocampus för icke-verbalt (bild-) minne. Majoriteten av patienter med TLE har en nedsatt minneskapacitet redan innan operation och denna kan tillta efter TLR.

Inför operation går patienten igenom en rad olika undersökningar. Dessa undersökningar syftar att hitta var i hjärnan anfallen startar och att utgöra underlag för bedömning huruvida vinsterna (anfallsfrihet) med operation står i relation till riskerna. Till dessa undersökningar hör neuropsykologisk bedömning (för att undersöka minne och andra kognitiva funktioner), MRI (för att hitta strukturella skador i hjärnan), funktionell MRI (fMRI) (för att undersöka sambandet mellan hjärnfunktion och lokalisation av hjärnaktivitet), samt EEG-undersökning (för att mäta hjärnans elektriska aktivitet genom elektroder som placeras utanpå huvudet eller inne i hjärnan). Ingen av metoderna kan på egen hand bedöma risken för minnesförsämring. Denna avhandling har undersökt olika aspekter av samtliga av dessa metoder.

Minnestester används för att undersöka patienters minnesfunktion innan och efter epilepsioperation. Totalt finns det en mängd olika minnestester och några av dem används för att mäta samma minnesfunktion, t.ex. verbalt minne. Ett normalt fungerande minne innan operation kan exkludera en patient från möjlighet att opereras p.g.a. att det då bedöms finnas en stor risk för försämrat minne efter operation. Omvänt bedöms en påvisad nedsatt minnesfunktion innan operation innebära att risken för ytterligare minnesförsämring är låg. Vikten av att använda tillförlitliga minnestester är således stor. I ett av delarbetena fann vi att de två mest använda testen för att mäta verbalt minne före och efter TLR i Sverige idag inte helt

och hållet mäter samma aspekter av verbalt långtidsminne och att ett av testen verkar vara påverkat av bildminnesfunktion. Detta talar för att vilket test som används kan påverka utfallet av utredningen, alltså om patienten kan opereras eller inte. Det betonar vikten av att noggrant utvärdera de neuropsykologiska minnestester som används. Det senare kan göras genom att i framtida studier följa upp och utvärdera minnesfunktion hos patienter som har genomgått TLR.

Med hjälp av strukturell och funktionell MRI undersöks hjärnans struktur och funktion inför TLR. Förekomsten av MRI-verifierade avvikelser (d.v.s. skador i hjärnan) ökar chansen för att en operation ska göra patienten anfallsfri. I ett av delarbetena fann vi med hjälp av en avancerad hippocampusundersökning (som innebär att omfånget av olika strukturer inom hippocampus mäts) att det föreligger olika samband mellan hippocampus olika delar och minnesfunktion. Vår förhoppning är att med denna teknik få mer fördjupad kunskap om det komplicerade förhållandet mellan olika hjärnstrukturer och minnesfunktion, och att denna kunskap på sikt ska kunna användas för att förbättra riskbedömning av minnesförsämring inför TLR. I ett annat av delarbetena undersökte vi om minnetestning med hjälp av fMRI kan ge information om risken för verbal minnesförsämringen efter operation. Vid uppföljning av patienter som hade genomgått TLR gav studien inte stöd för detta. Däremot visade det sig att språkbedömning med hjälp av fMRI synliggör förhållandet mellan språk och verbal minnesfunktion och på så vis ökar chanserna att värdera risk för verbal minnesförsämring efter operation.

I det sista delarbetet undersökte vi om en elektrod som under en kortare tid (ofta ett par dagar) opereras in i hippocampus, i syfte att hitta var i hjärnan anfallen startar i sig utgör en risk för försämrat verbalt minne. Vi undersökte patienter som under sin utredning inför TLR hade haft denna typ av hippocampuselektroder inopererade. Våra resultat visade att risken för verbal minnesförsämring var större hos den grupp patienter som hade haft hippocampuselektroder än hos kontrollgruppen som inte hade undersökts med denna typ av elektroder. Denna studie var den första i sitt slag att finna ett samband mellan hippocampuselektroder och verbal minnesförsämring, och vår konklusion av detta är att större studier behövs för att ytterligare befästa detta samband.

List of papers

1. A functional MRI-Based Model for Individual Memory Assessment in Patients Eligible for Anterior Temporal Lobe Resection. Maria Compagno Strandberg, Peter Mannfolk, Lars Stenberg, Hanna Ljung, Ia Rorsman, Elna Marie Larsson, Danielle van Westen, Kristina Källén. The Open Neuroimaging Journal. 2017; Vol. 11. pp. 1-16
2. Verbal memory decline from hippocampal depth electrodes in temporal lobe surgery for epilepsy. Hanna Ljung, Arto Nordlund, Maria Compagno Strandberg, Johan Bengzon, Kristina Källén. Epilepsia. 2017; Vol. 58, No. 12. pp. 2143-2152
3. 7 Tesla MRI for assessment of subregion-associated hippocampal memory deficits in TLE. Hanna Ljung*, David Berron*, Isabella M. Björkman-Burtscher, Maria Compagno Strandberg. Manuscript. **equal contributions*
4. Test-specific differences in verbal memory assessments used prior to surgery in temporal lobe epilepsy. Hanna Ljung, Maria Compagno Strandberg, Isabella M. Björkman-Burtscher, Elia Psouni*, Kristina Källén*. Epilepsy & Behavior. 2018; Vol. 87, 18–24. **equal contributions*

Abbreviations

AED	Anti-epileptic drug
ATL	Anterior temporal lobectomy
BNT	Boston Naming Test
BOLD	Blood oxygen level-dependent
BVMT-R	Brief Visuospatial Memory Test-Revised
CA	Cornu ammonis
CDT	Claeson-Dahl Test for Verbal Learning and Retention
DG	Dentate gyrus
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
IAT	Intracarotidal amytal test
HADS	Hospital Anxiety and Depression Scale
HS	Hippocampal sclerosis
ILAE	International League Against Epilepsy
LI	Laterality indice
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
mTLE	Mesial temporal lobe epilepsy
PET	Positron emission tomography
PCA	Principal Component Analyses
RAS	Risk assessment score
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
RMT	Recognition Memory Test
SAH	Selected amygdalohippocamectomy
SPECT	Single-photon emission computed tomography
Sub	Subiculum
SUS	Skåne University Hospital
T	Tesla
TLE	Temporal lobe epilepsy
TLR	Temporal lobe resection

Introduction and background

Epilepsy

Epilepsy is currently among the most common - and for society most costly – neurological diseases [1]. An epileptic seizure is an event of abnormal neuronal activity in the brain. The prevalence of epilepsy is about 0.7 % [2]. For the diagnosis of epilepsy, one out of the following conditions must be obtained according to the International League Against Epilepsy (ILAE): (1) at least two unprovoked seizures >24 hours apart, (2) one unprovoked seizure with a high risk (>60 %) of reoccurring seizures over a 10-year period, or (3) the diagnosis of an epilepsy syndrome. In the new classification of epileptic seizures, the underlying causes are classified as either genetic, structural/metabolic, or unknown [3].

Types of seizures

The classification of epileptic seizures is in its basic form established on the localization of seizure onset, i.e. either focal, generalized or unknown [3]. Focal seizures have, as the name implies, a localized focus of onset. Generalized seizures affect both hemispheres and large areas of the cerebral cortex simultaneously. Unknown onset refers to seizures where the origin is unknown, while the manifestations of seizures are recognized.

In its extended version, focal seizures are classified according to the patient's level of awareness, as seizures with either intact or impaired awareness, and in the next step as motor- or non-motor seizures. Since awareness is almost always impaired in generalized seizures, those are classified simply as motor- or non-motor (absence) seizures. All seizures, independent of their origin, are further classified according to clinical symptoms (e.g. tonic-clonic, myoclonic, epileptic spams etc.).

Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is the most common form of focal onset epilepsy [4]. TLE, in most cases, begins with some form of cerebral injury during infancy or early childhood. Most commonly, childhood febrile seizures or perinatal injuries, status epilepticus or head-injury including unconsciousness during any time of the life-span, is thought to be the cause of TLE [5]. Also, increasing attention has been directed

toward limbic encephalitis as a possible cause of TLE, as it presents with the same clinical symptoms as TLE, especially in late-onset TLE [6].

The pathophysiological course of epileptogenesis from the time of injury until the first seizure in TLE is uncertain, even though the extent of structural damage as well as inflammation, in acute and chronic seizures, seem to play a role. In the mesial syndrome of TLE, there is a latency period from the presumed insult until the first seizure [5]. It has been reported that mean age for debut of TLE is 15 years of age, and the onset is commonly defined as either early onset (often before the age of 17 or 18) or late onset [7,8].

Cognition in epilepsy

Cognitive deficits are common in patients with epilepsy, and so are psychiatric, behavioural and social cognition problems [9-11]. The sources of cognitive deficits are manifold, including both stable (e.g. etiology, age of onset) and dynamic (e.g. drug-regime, interictal- and/subclinical electroencephalography (EEG) manifestations) factors. Many times, there are individual combinations of factors affecting cognition in patient with epilepsy. Most commonly, cognitive deficits in epilepsy affect memory, attention, executive function or speed, or a combination of these.

Cognitive deficits are already present in patients with newly diagnosed epilepsies in both children and adults and, most likely, cognitive deficits and psychiatric problems precede the debut of the disease [12-15]. This challenges the long-standing assumption that epileptic seizures *per se* cause cognitive deficits in epilepsy, which was for a long time thought to be the case. This former viewpoint was based on the fact that cognition in epilepsy mainly was studied in patients with a chronic disease, e.g. candidates for epilepsy surgery. Since patients with longstanding or chronic epilepsies often have an early disease onset, a more probable explanation for the observed cognitive deficits is some form of obstruction early in life, resulting in an accumulative negative effect on neurodevelopment [11].

Structural lesions are present in a large proportion of both children and adults with epilepsy [16,17]. These can be associated with either specific or more general cognitive dysfunction, depending on the localization of the lesions and at what time in life the damage occurred.

Cognitive deficits can also be accentuated by other factors, such as e.g. anti-epileptic drugs (AEDs). Some drugs have shown to have particularly adverse effects on cognition, but also the total drug load will have negative neuropsychological consequences [18,19].

One of the most frequent complaints from patients concerning problems related to the epilepsy and to the AEDs are subjective memory problems. These reports have

shown to have weak correlation to objective episodic memory performance. Instead, subjective memory complaints in epilepsy seem to be related to patients' mood and to other cognitive problems, such as language deficits, and also to the total drug load [20,21].

Memory

Hippocampus

Eighty percent of patient with TLE have seizures originating from the hippocampus of either the left or the right hemisphere, or both hemispheres [4]. Figure 1 shows a 7 Tesla magnetic resonance imaging (MRI) scan, T2 weighted image (0.5*0.5*0.75 mm axial, 0.5*0.5*0.75 mm coronal) of a patient with TLE and a left hippocampal sclerosis.

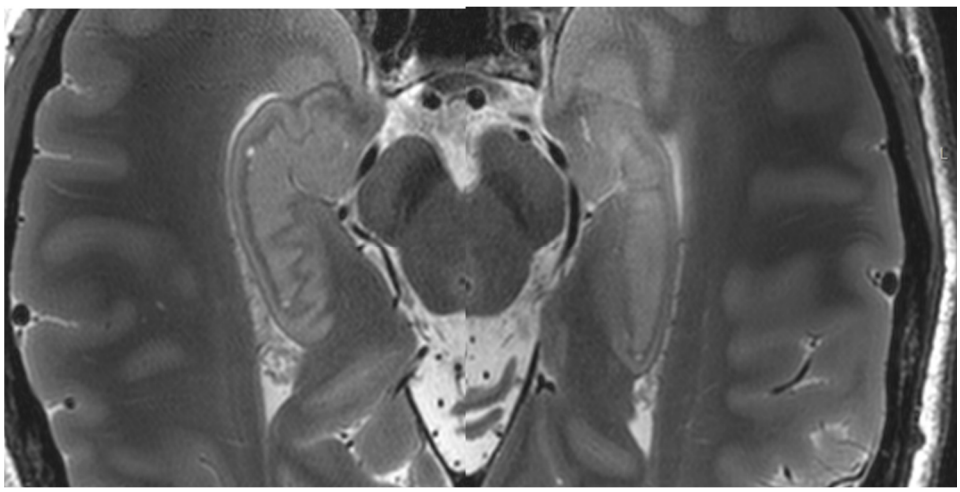

Figure 1
Axial images of the hippocampus in a patient with left sided mesial sclerosis. Courtesy of I. Björkman-Burtscher, Dept of Radiology, University of Gothenburg, Sahlgrenska Academy

The hippocampus is part of the medial temporal lobe and the limbic system. The hippocampus is usually divided into the subregions cornu ammonis 1-3 (CA1-3), the dentate gyrus (DG) and the subiculum (Sub). However, there is no consensus regarding which subregions to include in the hippocampal formation nor where to draw the anatomical borders for each respective subregion [22,23]. Figure 2 shows an image of an automated segmentation, including all subregions of the right hippocampus, in a patient with TLE.

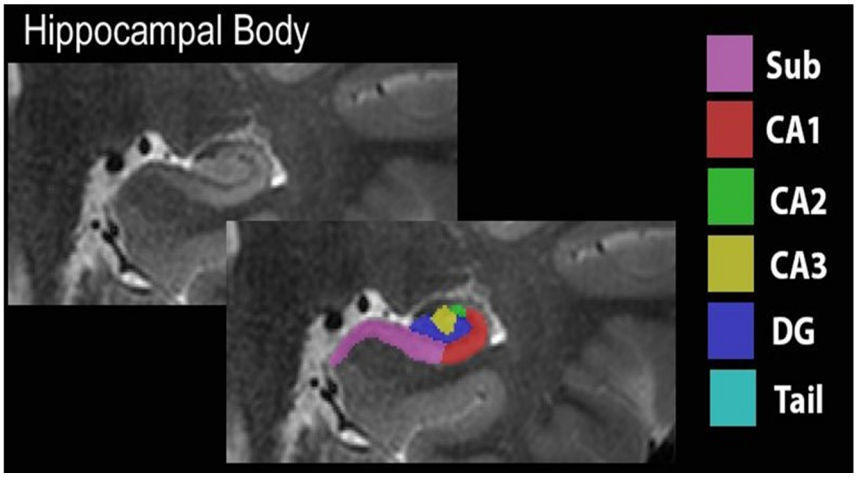

Figure 2
Hippocampal body including all subregions. Courtesy of D. Berron, Clinical Memory Research Unit, Department of Clinical Sciences, Lund University

Lesions in the hippocampus, e.g. cell loss in the case of hippocampal sclerosis (HS) in TLE, are associated with memory impairment [24,25]. HS in TLE is defined by loss of principal cells and of interneurons, structural changes concerning sprouting and neurogenesis, gliosis, disruptions of blood-brain barrier integrity and neuroinflammation [5]. Patients with TLE display variations in neuron loss. Histopathological specimens of resected tissue confirm HS in 34 - 45 % of all resected epilepsies, and in up to 60 % of all epilepsies with a mesial TLE (mTLE) [26]. Microscopic inspection of resected tissue after temporal lobe resection (TLR) has demonstrated that cell loss in the CA1 is most characteristic for the mTLE, while large variations of neuron loss in the CA2 exist, and that the structural integrity of the CA3 and the DG are least affected [27]. As for memory function, some regions of the hippocampus, e.g. the CA1 and CA3, seem to be of greater relevance than others, although no real consensus exists regarding this [28].

Declarative episodic memory

In 1972, Tulving made a categorization of different types of long-term memory (LTM), into *semantic* and *episodic* memory, and stated that these memory types were distinct from each other and involved different memory systems [29]. Semantic memory represents the acquisition and storing of things that we learn (e.g. “Madrid is the capital of Spain”), while episodic memory represents things that we experience (e.g. remembering the first day of school). Both semantic and episodic memory are forms of declarative, or explicit, memory. Figure 3 shows a proposal to the memory taxonomy.

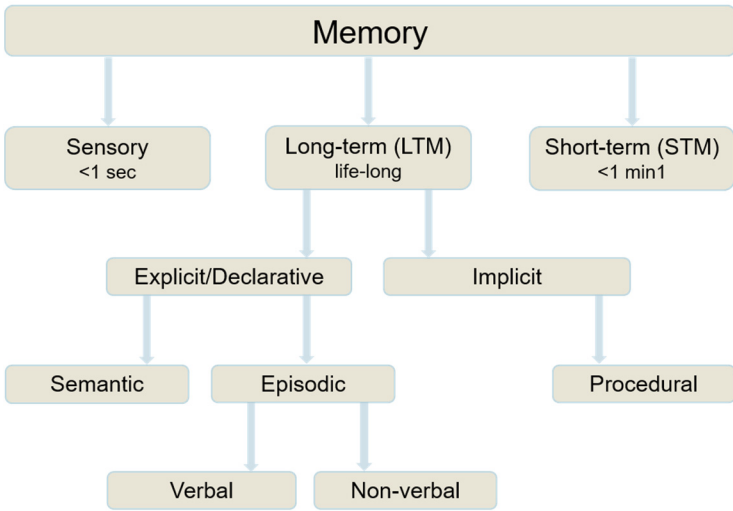

Figure 3
Taxomony of memory. Image source: H. Ljung, 2018

The role of the hippocampus for declarative episodic memory is well-known, much because of the important work of Scoville and Milner in the 1950s on material-specific memory deficits in patients with TLE and structural lesions [24]. The hippocampus is involved in both encoding of new information and retrieval of already learnt information, although the latter has been shown to be more dependent on hippocampal structures than the first [30,31]. The hippocampus seems to be responsible for integrating input from numerous brain regions and storing that information into entities to be remembered, as declarative episodic memory. While declarative episodic memory is impaired as a consequence of hippocampal damage, semantic memory is fairly preserved [32].

Memory in TLE

TLE is highly associated with deficits in episodic memory [33-35]. Some studies show that up to 70 % of all patients with chronic TLE have impaired memory, while others have differentiated between three phenotypes of patients with TLE exhibiting diverse patterns of cognitive impairment: minimally impaired cognition (47 %), memory impairment alone (24 %) or memory impairment combined with impaired executive functions and speed (29 %). These phenotypes have also shown to be related to differences in cortical thickness and brain volume [36]. It should be underlined that differences in proportion of patients reported to have memory deficits might partly be explained by diversity in the measures that have been used for testing memory function. Nevertheless, this demonstrates that cognitive

impairment in TLE goes beyond memory and that patients with TLE are not a homogenous group. What is evident is that there does not seem to be a progression of memory deficits over the course of the disease, since the gap in memory performance between patients with TLE and healthy controls doesn't become wider with time [37-39]. Rather, it has been suggested that in TLE, a hindrance in development is established early in life, even before seizure onset.

Epilepsy surgery

About 70 % of all patients with epilepsy become seizure-free on AEDs [40]. Seizure freedom is almost exclusively obtained after trying one or two drugs [41,42]. Despite the introduction of multiple new AEDs with different pharmacological mechanisms of action, the chance of seizure-freedom has not increased over the last decades [43].

A large proportion of the 30 % of patients which are *not* seizure-free from AEDs have either focal or unknown origin of seizure onset. As of today, epilepsy surgery is the only long-lasting curative treatment for epilepsy. For non-seizure-free patients, so called therapy-refractory patients, surgery means a chance of a life without an otherwise life-long disease. Up to 70 % of adults, and a slightly higher percentage of the paediatric population, obtain long-term seizure freedom from surgery [44,45]. Since epilepsy surgery is not without risks, e.g. post-surgical infections, hematomas, mono-/hemiparesis or cognitive deficits, the selection of eligible patients is crucial [46,47].

Temporal lobe resection

TLE in general entails a high risk for therapy resistance compared to other types of epilepsy [48]. Eighty percent of seizures in the temporal lobes originate from the hippocampus of either the left or the right hemisphere, or from both hemispheres [4]. Temporal lobe resection (TLR) is the most common form of epilepsy surgery in adults (73 % of all cases), followed by extra-temporal lesionectomies. TLR, under the most successful circumstances, results in long-term seizure freedom in about 70 % of all cases [5,48,49].

TLR is in most cases performed as anterior temporal lobectomy (ATL), i.e. resection of 3 - 6 cm of the anterior temporal lobe, including the hippocampus and parts of the amygdala [50]. The extent usually depends on whether the resection is done in the language dominant temporal lobe or not and whether there is a lesion or not. An alternative approach to ATL is so called selected amygdalohippocamectomy (SAH), in which temporal neocortex and white matter is spared. Few differences with regard to post-surgical seizure outcome have been reported between the two methods,

while SAH has been shown to be more lenient with regard to post-surgical memory deficits [51].

Memory pre- and post-temporal lobe resection

The majority of patients that undergo TLR demonstrate memory deficits prior to surgery. These deficits can, however, be aggravated by surgery, and deterioration in verbal memory is seen in over 60 % of patients after left TLR and in about 25 % of patients after right TLR [52,53]. A normal pre-surgical memory capacity indicates a higher risk for memory deterioration due to surgery, especially in the case of resection in the language-dominant temporal lobe. Studies on long-term effects on memory after TLR show a stable outcome after two, and up to ten, years after surgery [54]. Progressive post-surgical memory deterioration occurs more often when seizure freedom is not achieved [55]. These patients have been described as ”double-losers”, in that they don’t become seizure-free from surgery and they have a higher risk for post-surgical memory deficits. Many patients eligible for TLR are at a point in life were education, job-advancements and starting a family is central. An added memory deficit from surgery can have large consequences on everyday life for these patients.

Presurgical investigations

The chance of achieving seizure freedom, and the risk of postsurgical deficits, are evaluated during the extensive pre-surgical work-up. Patients with an epilepsy of presumed focal onset can be considered for surgical work-up after having tried two or more AEDs in sufficient doses without achieved seizure-freedom.

The presurgical investigation consists of, in its most basic form, extracranial video-electroencephalogram (EEG), structural MRI and neuropsychological assessment. Lateralization of language using fMRI is applied in close to all adult patients in the surgical program at Skåne University Hospital (SUS).

If patients are MRI-positive (i.e. they show pathology on the MRI) and when EEG manifestations and the neuropsychological assessment show concordant results, the choice of offering patients surgery or not is usually straightforward. If MRI is not accordant with EEG and neuropsychological assessment, or if the patient is MRI-negative (i.e. they don’t show pathology on the MRI), other methods such as invasive EEG, single-photon emission computed tomography (SPECT), positron emission tomography (PET) or magnetoencephalography (MEG) can be evaluated to gather further information.

The pre-surgical evaluation is presented in the flow-chart in Figure 4, showing where in the pre-surgical investigation the studies in the thesis belong.

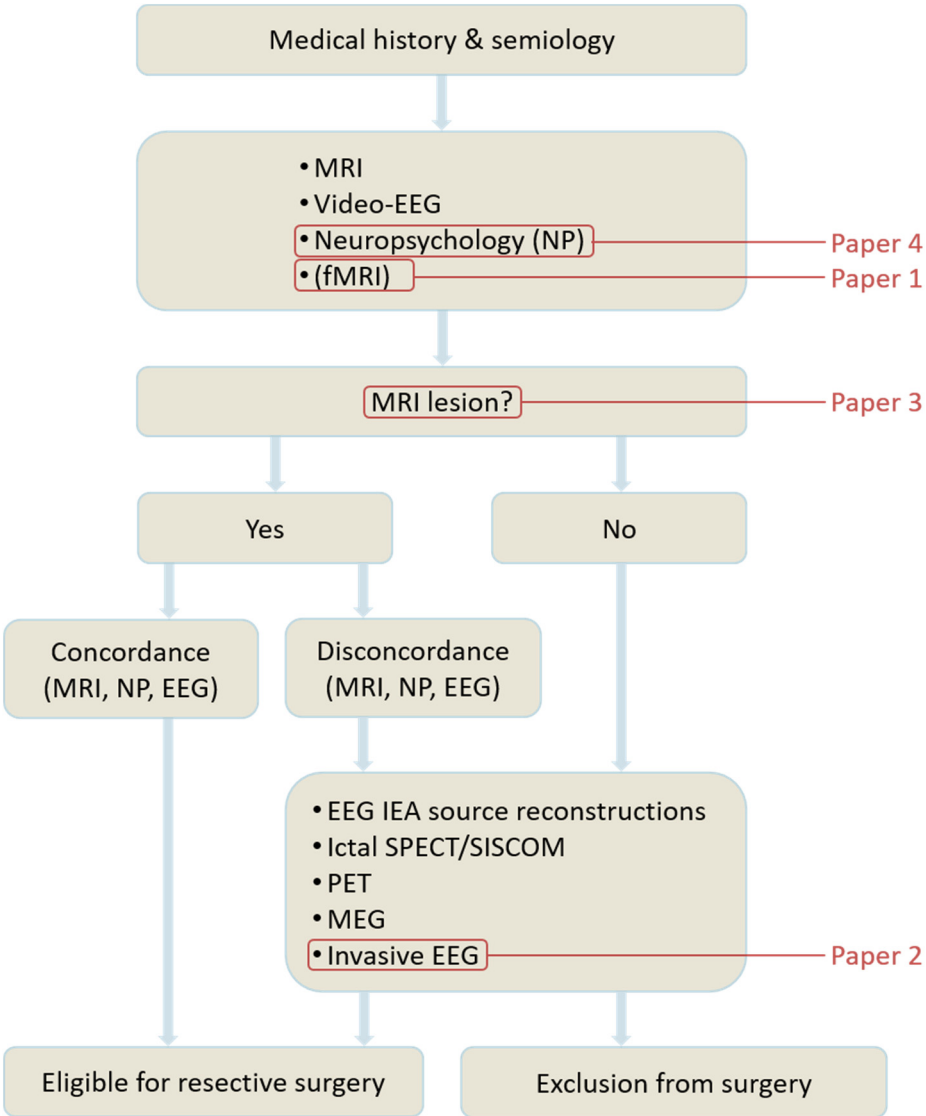

Figure 4
Flow-chart of pre-surgical work-up for epilepsy surgery. Adopted from K. Källén, Division of Clinical Sciences Helsingborg, Department of Clinical Sciences, Lund University

1.3.2.1. Neuropsychological memory assessment

In the neuropsychological assessment of patients with epilepsy, testing memory function is central. Verbal memory tests have high ecological validity, in contrast to e.g. self-reported memory deficits, and memory problems affect many aspects of everyday life [56].

Episodic memory is assessed by testing both verbal material (i.e. verbal memory) and visuo-spatial material (i.e. non-verbal or visuo-spatial/visual memory). Generally, both encoding (or learning) and recall (or retention) are assessed for both verbal and non-verbal memory. The logic behind this is that episodic memory in the adult brain is material-specific, with verbal memory being associated to the language-dominant (often left) temporal lobe, and non-verbal memory to the non-language-dominant (often right) temporal lobe. This viewpoint has dominated the field of epilepsy research and epilepsy surgery for decades [57,58]. However, with today's knowledge, the material-specific view is by some considered to over-simplify distribution of language and memory. However, it is still the frame-work for a lot of the work on memory in epilepsy [59]. For example, the fundamental assumptions in memory assessment in the pre-surgical work-up are based on the concept of *functional adequacy* and *reserve capacity* [60]. The first refers to the function of the epileptogenic temporal lobe and the tissue to-be-resected. A good baseline performance, indicating normal or mainly non-affected memory performance, increases the risk of post-surgical memory decline. The reserve capacity refers to the function in the contralateral, i.e. non-inflicted, temporal lobe. This latter represents what the patient "is left with" in terms of (memory) function after surgery.

Neuropsychological tests need to be robust regarding their psychometric properties. In other words, they need to assess what they are constructed to assess. Nonetheless, different memory tests designed to, and clinically used for, measuring the same aspects of memory (e.g. verbal memory) do not necessarily use the same measurements [61,62]. For example, the material to be remembered can be either related or unrelated words or stories (in verbal memory tests), or e.g. faces or pictures (in non-verbal memory tests). This allows for different test-specific mnemonic strategies, potentially making tests unequally sensitive for measuring memory. When comparing test results from studies on patients with epilepsy, this needs to be considered. This issue gets even more intricate since epilepsy centers, both in Europe and the United States, use a variety of memory tests in patients with epilepsy [63,64].

From here on, declarative episodic memory will be referred to solely as *memory*, or distinctively as *verbal memory* and *non-verbal memory*.

Electroencephalography (EEG)

Extracranial (scalp) EEG is used for detecting seizure onset in epilepsy in general, and in work-up for TLR. In about 30 % of all pre-surgical investigations, onset of focal seizures cannot be determined by scalp EEG, and invasive EEG monitoring then becomes an important part of the pre-surgical investigation. Mesial temporal lobe coverage is important in patients with TLE, since most of these seizures originate from medial temporal lobe regions. For this purpose, subdural strips or

depth electrodes are used. Depth electrodes can be placed uni- or bilaterally according to a parasagittal or orthogonal approach as shown in Figure 5 [65,66]. Parasagittal placement of depth electrodes lets the electrode penetrate the hippocampus longitudinally, whereas the orthogonal approach lets it enter the hippocampus laterally. It has been shown that depth electrodes are associated with fewer surgical risks than e.g. strip electrodes [67]. However, the risk of neuropsychological effects from depth electrodes has not been systematically studied and is not fully understood.

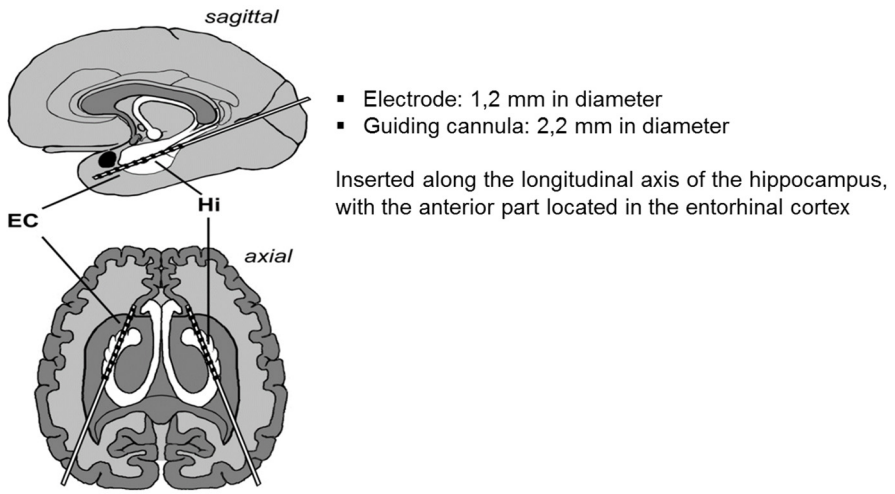

Figure 5
Image source: Mormann *et al.*, Front Hum Neurosci, 2008 (66)

Magnetic Resonance Imaging (MRI)

Structural MRI has revolutionized epilepsy surgery, as source of information on epileptogenic lesions and as predictor of surgical outcome in epilepsy surgery. MRI provides images from multiple planes and with a thickness as little as down to 0.5 mm.

A systematic review on surgical outcome following TLR reported non-lesional (MRI-negative) TLR resulting in seizure-freedom in about 45 % of all cases and lesional (MRI-positive) TLR in about 69 % of all cases [68]. This concludes that pathology shown on MRI, and the structural integrity of the hippocampus, is an important indicator for surgical outcome in terms of seizure-freedom and for post-surgical memory outcome. The pre-surgical structural integrity of the hippocampus is highly essential for the prognosis of the disease, as well as for surgical result in terms of seizures and memory performance [68,69]. The structural integrity of the tissue

to be resected is the base for the concept of "functional adequacy", a well-established notion that the memory function in the presurgical hippocampus of interest is an important predictor for post-surgical memory outcome [70].

With increased magnetic field strength, previously undetected pathology, or inconclusive MRI results, can be found. In patients with focal refractory TLE using a recommended 3 Tesla (T) MRI protocol for surgical investigations for TLR, it has been shown that about 20 % more cases of previously undetected pathology is observed [71].

Advances in ultrahigh-field MRI techniques, with e.g. the utilization of 7T MRI, are starting to show promising results for improved detection of mesial sclerosis and other epileptogenic foci, although the number of studies, at this point in time, are limited and the protocols used are not harmonized [72,73]. This is a significant matter, since it has been shown that histopathology reveals pre-surgically undetected mesial sclerosis in up to 50 % of all MRI-negative patients [74,75]. In our own epilepsy surgical unit at SUS, histopathological evaluation of 31 patients having undergone TLR between 1998 and 2009 demonstrated undetected mesial sclerosis in one third of the total cohort (unpublished data).

Functional MRI for lateralization of language

Functional MRI (fMRI) is a non-invasive method for detection of neural correlates to mental functions (e.g. language). It uses so-called blood oxygen level-dependent (BOLD) changes in the MRI-signals. Neural activity increases in the brain region that is being activated by mental tasks. This increases the need for oxygen in the active brain regions, leading to alternations in blood flow. Thus, the relations between the amount of oxygenated arterial blood and the non-oxygenated venous blood change.

The sequence of stimuli is called an fMRI paradigm, and how the paradigm is designed is based on the mental function that is studied. Two common types of paradigms are the block design or the event-related design paradigm. In a block design paradigm, stimuli are presented continuously over a period of time (a block) to maintain the mental activity. These blocks of increased neuronal activity (when tasks are being performed) are separated from blocks of inactivity (when tasks are not being performed). In an event-related design paradigm, stimuli (events) are presented for much shorter periods of time.

Language lateralization prior to TLR is important for two reasons. First, TLR in the language-dominant temporal lobe has a much greater negative impact on verbal memory than TLR in the non-language-dominant temporal lobe. Second, atypical language dominance is more common in patients with epilepsy than in the general population [76,77]. This includes both reorganization of language to the contralateral lobe, and bilateral temporal lobe involvement for language out- and input.

Especially patients with left TLE including structural abnormalities have demonstrated re-lateralized language function [67,71]. Further, language function in areas with pathology can be re-lateralized to the contra-lateral lobe, while in the same patient language function away from pathology can be spared and remain within the ipsilateral lobe.

Language lateralization using fMRI has, especially over the last two decades, shown to be a valid predictor for language-dominance. In Europe, it is used for lateralization of language in most epilepsy surgery centers [63,71].

Results from language MRI have in most cases shown over 90 % concordance with results from the intracarotidal amytal test (IAT), or the so-called Wada test, which was previously known as gold standard for language mapping [78-80]. Language fMRI is, compared to e.g. the IAT, a non-invasive, inexpensive and more easily repeatable procedure. Expressive language is often assessed with a verbal-fluency test and a verb-generation test, and language comprehension with a reading-comprehension test.

Aims

The aim of this thesis was to evaluate the tools used in pre-surgical work-up for TLR to predict post-surgical memory outcome and to improve selection of patients eligible for TLR.

The specific aims were:

Paper 1

To study if presurgical fMRI memory paradigms add information on the risk of verbal memory decline after anterior temporal lobe resection.

Paper 2

To investigate the possible negative effect of longitudinal hippocampal depths electrodes, used for localization of seizure onset, on verbal memory.

Paper 3

To investigate if declarative episodic memory in TLE patients correlates to hippocampal subregional volumes, segmented from 7T MRI images.

Paper 4

To study the structural concordance between two commonly used verbal memory tests used for pre-surgical work-up in TLR, and their relations to non-verbal memory, demographics and epilepsy-related factors, as well as their correspondence with mesial sclerosis.

Patients and methods

Patient selection

The patients in the studies were all patients at the Department of Neurology at Skåne University Hospital (SUS) in Lund, Sweden, between the time of 2003 and 2017. All patients had either a therapy-refractory or a difficult-to-treat TLE, and the majority of the patients had been candidates for TLR or had undergone TLR during this time period. All patients had, either due to subjective complaints of deficits in memory, or as a part of their evaluation for TLR, undergone one or more neuropsychological assessment/assessments.

Paper 1

This study examined whether fMRI memory paradigms applied in the pre-surgical investigation for TLR provided additional information on the risk of post-surgical memory deterioration. Twenty-four patients with therapy refractory TLE, eligible for TLR either at SUS (n=19), Sahlgrenska University Hospital (n=4) or Uppsala University Hospital (n=1), were initially included in the study. All patients had undergone at least the standard basic evaluation for epilepsy surgery including extracranial EEG-monitoring, MRI-scanning and neuropsychological assessment (further described under 3.2. Neuropsychological assessments). The decision for or against surgery was made during a conference consisting of specialists from multiple clinical disciplines. Fourteen patients (right TLE: n = 6; left TLE: n = 8), prior to proceeding to surgery, completed a fMRI task including a verbal memory encoding paradigm and a non-verbal recall paradigm.

Based on the results from each patient's structural MRI, neuropsychological assessment and the language dominant hemisphere, an individual risk assessment score (RAS) was created. The RAS was used as an indication for the risk of post-surgical verbal memory decline, and each of the predictors (structural MRI, neuropsychology and language fMRI) was weighted as equally important indicators. The RAS was created as follows: (1) positive MRI evaluation gave 0 points (indicating low risk for post-surgical memory decline), while negative MRI evaluations gave 1 point (indicating high risk for post-surgical memory decline); verbal memory capacity equal to or less than 1 SD below the normative range gave

0 points (indicating low risk for post-surgical memory decline), while a memory score within the normative range gave 1 point (indicating high risk for post-surgical memory decline); presumed language dominance in the not-to-be-resected temporal lobe gave 0 points (indicating low risk for post-surgical memory decline), while presumed language dominance in the to-be-resected lobe gave 1 point (indicating high risk for post-surgical memory decline). Patients with a total RAS of 0 - 1 points were assumed to have a low risk for post-operative verbal memory decline, while patients with 2 - 3 points were assumed to have a medium to high risk for post-surgical verbal memory decline.

The fMRI memory paradigms included one experimental verbal memory paradigm and one non-verbal memory paradigm that had previously been used at other epilepsy surgery centers [81,82]. The results from the fMRI memory paradigms were not included in the clinical assessments. In an event-related designed paradigm for verbal memory, the patients performed a verbal encoding test and were asked to, alternately, decide if the words that they saw in the MRI-scanner were a) either pleasant or not, or (b) if the underlined letters in the words they saw in the MRI-scanner were in alphabetical order or not. The first task was thought to represent deep encoding of verbal learning, and the latter to represent shallow encoding of verbal learning [8384]. The non-verbal memory paradigm was a block-design paradigm, including a mental navigation task called the Roland Hometown Walking Test [85]. In this task, patients were asked to recall a well-known walking tour in their own hometown, dived into different phases. An unexpected recognition test followed the fMRI verbal memory paradigm, immediately after the scanning session, aiming at testing for incidental learning.

The verbal memory fMRI paradigm was designed to be equivalent to a clinically used verbal memory test, namely the Claeson-Dahl Test for Verbal Learning and Retention (CDT). The non-verbal memory fMRI paradigm was considered to reflect a clinically used non-verbal memory test, namely the Rey Complex Figure Test (RCFT).

Post-surgical structural MRI (median 6 months, range 2 - 15.5) and post-surgical neuropsychological assessment (median 6 months, range 3 - 20) were performed. A change in memory scores equal to, or larger than, 0.5 SD was judged as a minor improvement or a minor deterioration (i.e. changes ranging from 0.5 to 0.9 SD). A change equal to, or larger than, 1 SD was considered a major change. Post-surgical memory change was compared to pre-surgical memory fMRI results to evaluate if the memory fMRI added useful information on risk for post-surgical memory outcome.

Paper 2

This paper studied possible negative effects from longitudinal hippocampal electrodes on verbal memory. A long-term neuropsychological follow-up (up to 10 years) was performed in patients with therapy-refractory temporal lobe epilepsy, once candidates for TLR at SUS. Patients were divided into two groups, a study group and a control group, based on whether or not they had received longitudinal depth electrodes for seizure onset detection during their work-up before surgery. Patients with an IQ lower than 60 or with an ongoing psychiatric or a progressive disease other than TLE were deselected. Also, patients that had received surgery in the left temporal lobe were excluded. The reason for this was that in this study, the possible negative effect from hippocampal depth electrodes on memory was to be investigated, and not the effect on memory from surgery. Patients that later received surgery in the right temporal lobe were, however, included, since the main purpose was to study possible *verbal* memory deficits. The study group comprised patients examined with longitudinal hippocampal depth electrodes in the language-dominant hemisphere, while the control group comprised patients with no invasive electrode placement during their pre-surgical work-up.

Seventeen patients were eligible for the study group, and 16 patients finally gave their consent to participate in the study. Out of these 16 patients, all except one had received bilateral depth electrodes. Seventy-one patients were initially eligible for the control group, and 24 were finally included after a thorough selection based on their resemblance to the study group, shown in Figure 6. The factors that were evaluated, when selecting the control group, were factors that could possible affect memory, namely (in descending order): right TLR (yes/no); seizure freedom (yes/no); biological age (± 10 years vs. respective individual in the study group); age at epilepsy onset (below or above 18 years of age); education; and duration of epilepsy.

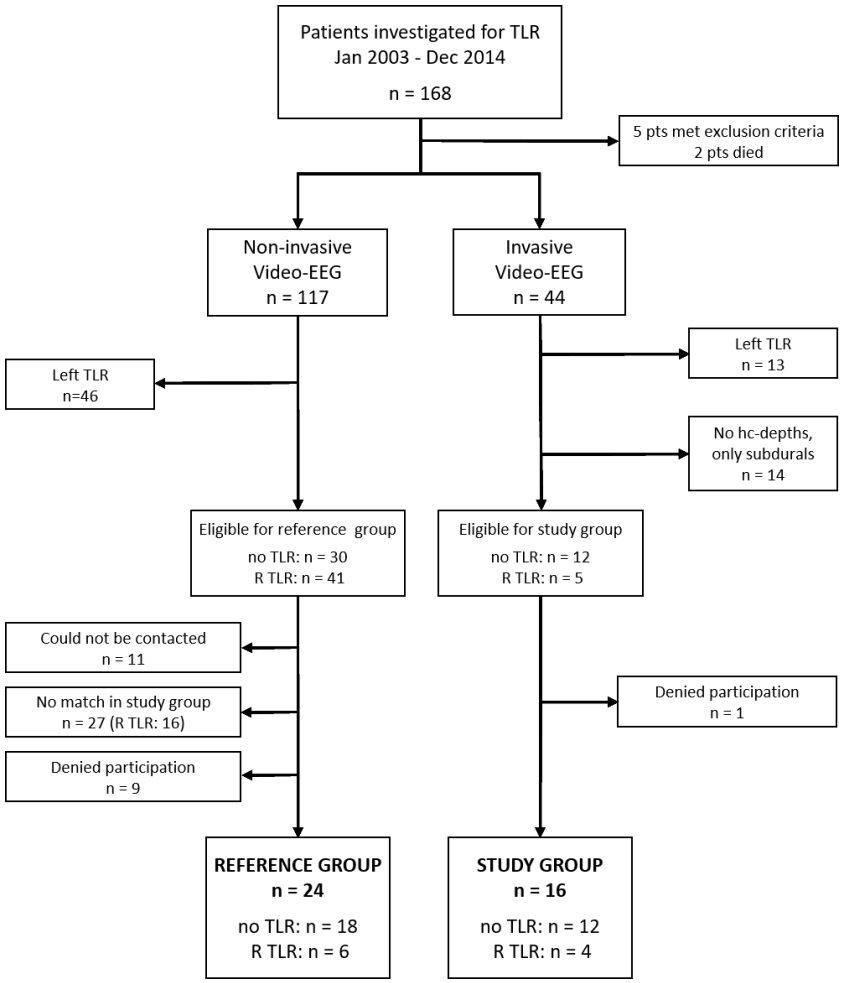

Figure 6
Patient selection. Source: Ljung *et al.*, Epilepsia, 2017

All patients underwent a neuropsychological assessment, with emphasis on memory capacity, after inclusion in the study (this is further described under 3.2. Neuropsychological assessments). This memory assessment was compared to the pre-surgical memory performance, both individually and on a group level.

Paper 3

This study investigated if declarative episodic memory correlates with hippocampal subregional volumes and whether visual detection of pathology using 7T MRI corresponds to memory deficits in patients with TLE. Inclusion required that

patients with TLE had undergone neuropsychological assessment, either during work-up for TLR or for other clinical reasons, demonstrating unilateral or bilateral memory impairment ≥1 SD below the normative mean. The neuropsychological assessment is further described in 3.2. Neuropsychological assessments. All patients, except two, had previously undergone a 3T MRI investigation for reasons related to their epilepsy. Exclusion criteria were age <18 years, ongoing psychiatric or progressive neurological disorder other than multiple sclerosis in addition to TLE (n = 2), resective temporal lobe surgery or treatment with topiramate or zonisamide. This left a total of 22 patients that agreed to participate in the study.

All study patients were examined by a 7T MRI scan. All (previous) 3T MRI and 7T MRI scans were evaluated by the same radiologist, following the same protocol. The following structures were assessed for both temporal lobes: 1) reduced hippocampal volume, 2) increased hippocampal signal, 3) anterior and/or posterior hippocampal pathology, 4) mesial sclerosis, 5) non-hippocampal epileptogenic lesion and 6) non-epileptogenic lesions. The 3T MRI scans had been assessed for an earlier study [86]. 7T MRI scans were assessed in the present study, using the same protocol.

Automated segmentation of hippocampal subfields technique was used for dividing the hippocampus into its anatomical subregions CA1-3, DG and Sub [87,88].

Paper 4

This paper aimed at comparing the construct structure between two verbal memory tests in presurgical evaluation for temporal lobe epilepsy (TLE) in Sweden, the Claeson-Dahl Test for Verbal Learning and Retention (CDT) and the Swedish version of the Rey Auditory Verbal Learning Test (RAVLT). Patients with a diagnosis of TLE were included if they had performed memory assessment with two verbal memory tests, the Claeson-Dahl Verbal Learning and Retention Test (CDT) and the Swedish version of the Rey Auditory Verbal Learning Test (RAVLT). After excluding four patients due to mental retardation, 59 patients remained. Out of these, 57 had been evaluated for TLR at the epilepsy surgical center at SUS, between 2010 and 2017, and the remaining two had been neuropsychologically evaluated due to subjective memory problems. Neuropsychological test data were retrieved from the patients' medical records. The neuropsychological assessment is further described in 3.2. Neuropsychological assessment.

For assessment of mesial sclerosis, 3T MRI examinations were reviewed by a neuroradiologist who was blinded for clinical data. MRI examinations of satisfactory quality, and performed closest in time to neuropsychological assessment, were included and scored according to: (1) presence of mesial sclerosis (yes or no) based on anatomy, volume and signal of the hippocampus; (2) presence

of epileptic lesions in the temporal lobe other than mesial sclerosis (yes or no) or outside the temporal lobe (yes or no); (3) presence of lesions not associated to epilepsy (yes or no).

Neuropsychological assessments

Studies 1 and 3 included prospective neuropsychological data. Study 2 included both historical and prospective neuropsychological data, while study 4 contained only historical data. In all four studies, the entire memory test battery was administered in one session per patient. In most cases, the tests were presented systematically and in the same order, with no verbal or non-verbal memory tests overlapping during the assessment. An exception from this rule were cases of incomplete historical test data, due to individual patient-related circumstances.

The foundation for the neuropsychological assessment was as follows: for verbal memory, the CDT (studies 1 - 4), the RAVLT (studies 2 - 4) and the Logical Memory from the Wechsler Memory Scale (WMS) (study 2) were used. For non-verbal memory, the Rey Complex Figure Test (RCFT) (studies 1- 4), the Brief Visuospatial Memory Test-Revised (BVMT-R) (studies 2 - 4) and the Recognition Memory Test for Faces/the Warrington (RMT/Warrington) (studies 2 - 4) were used. Studies 2 and 4 also included a verbal naming test, the Boston Naming Test (BNT), and a self-assessment measurement for symptoms of anxiety and depression, namely the Hospital Anxiety and Depression Scale (HADS).

Verbal memory tests

The CDT is a Swedish verbal memory test for list-learning and recall [89]. It consists of a 10-item wordlist which is read to the test person (i.e. the patients) at a maximum of ten times, or until it is repeated correctly twice by the patient. After 30 minutes, the patient is asked to repeat the words from the wordlist, a task that the patient is unaware of in advance. The wordlist contains eight abstract words (adjectives, verbs, pronouns, relative pronouns, conjunctions and adverbs) and two concrete words (nouns).

The Swedish version of the RAVLT contains a 15-item wordlist, all nouns, which are read to the patient five times, and asked to be recalled by the patient each time after the entire list has been read [90]. After a brief distraction by another wordlist, the patient is asked (not being aware of this task in advance) to recall the 15-item wordlist and then to do the same thing once again after 30 minutes.

The WMS Logical Memory consists of two short stories that are read to the patient, one at a time [90]. After each story has been read, the patient is asked to recall as many details as possible from the stories (the first story on one occasion and the second story on two occasions), and then to recall both stories once again 30 minutes later.

The CDT, the RAVLT and the WMS Logical Memory subtest have all shown to be sensitive to verbal memory problems in patients with TLE, and they are used for pre- and postsurgical evaluation [54,62,91,92].

Non-verbal memory tests

In the RCFT, the patient is asked to copy a complex figure by drawing it. The patient is then asked to recall the figure by drawing it again after 3-5 minutes and then a last time after 30 minutes [93].

The BVMT-R contains six simple geometric figures which are presented to the patient over three consecutive learning trials (all lasting 10 seconds), and asked to be recalled, by drawing them, after each trial and then again after 30 minutes [93].

In the RMT/Warrington, the patient is presented with 50 male faces, each face shown for approximately 3 seconds [93]. Immediately after seeing all faces, the patient is asked to recall which faces have been shown in a multiple-choice test.

All three non-verbal memory tests have previously been used in patients with TLE and to detect nonverbal memory deficits following right TLR [94-96]. However, the Warrington is the only of the non-verbal memory tests that has shown consistent results in detecting non-verbal memory deficits in patients after TLR in the non-language dominant temporal lobe.

Additional neuropsychological and psychiatric measures

Verbal capacity, in terms of naming ability, was assessed using the Swedish version of the Boston Naming Test (BNT) [97]. In this test, the patient is presented with pictures of familiar kind and with increasing difficulty and asked to name the object in the picture within a period of 20 seconds.

The HADS, a self-report questionnaire with 16 questions on symptoms of anxiety and depression, was used to screen for psychiatric problems [98].

Statistical analyses

All data were analysed using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA) and SPSS 22 and SPSS 25 (IBM Corp., Redmont, WA, U.S.A.), SPM5 software (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm), MATLAB (Mathworks, Natick, MA, U.S.A.)

In study 1, the course of the blood-oxygen level dependent (BOLD) signal in fMRI was modelled by combining onset vectors from each paradigm with the canonical hemodynamic response function. To estimate regions of interest, laterality indices (LIs) were calculated with a toolbox functioning within the SPM5 environment (Wilke 2007), during the verbal memory fMRI paradigm. An overall fMRI LI mean >0.1 was classified as typical/left lateralization, while a LI mean <-0.1 was classified as atypical/right lateralization. A LI mean between these two cut-offs was classified as bilateral/non-lateralized. For the statistical analysis of neuropsychological data and fMRI data, multiple regressions and Spearman correlations were calculated.

In study 2, statistical comparisons were performed with Student's t-test for both between- and within-group comparisons. For test data that were not normally distributed, the Mann-Whitney U-test was used. Effect sizes were expressed as Cohen's d. A change of ≥1 SD was defined as clinically significant, using age- and education-related normative reference data [89,93]. To examine whether possible confounders (e.g. biological age >50 years, right TLR and bilateral TLE) had influenced the results, a logistic binary regression was performed.

In study 3, correlations between the automated calculated volumes of hippocampal subregions, as well as volume of the left hippocampus, volume of the right hippocampus and the combined volume of both hippocampi, and memory performance (the latter transformed into z-scores) were calculated using linear regression analyses. Verbal memory deficits and non-verbal memory deficits were related to the visual MRI inspections. These were demonstrated as concordant or disconcordant.

In study 4, two Principal Component Analyses (PCA), using Varimax rotation (Kaiser normalization), were performed. In the first, common features and dissimilarities between the CDT and the RAVLT (using z-scores) were investigated, using memory test variables from these two tests. From this analysis, factor scores were calculated based on the derived components. In the second PCA, separate and common features between both verbal memory variables (from the CDT and the RAVLT) and non-verbal memory variables (from the RCFT, the BVMT-R and the RMT/the Warrington) were analysed, again using z-scores. There were 59 cases of valid data (i.e. individual patients' memory scores) and 15 memory variables. This rendered the sample just about adequate, and therefore the results from the PCAs

are considered preliminary. The Bartlett's test of sphericity was used to determine the suitability of the database for data reduction, and the Kaiser-Meyer-Olkin measure for the overall data set was used to assess adequacy for each analysis. Further, Pearson's correlation analysis was used to investigate relations between factor scores from the components constructed by CDT and RAVLT variables (the first PCA). Relations between the verbal memory components and the non-verbal memory components were examined to investigate their overlapping and common features. Also, relations between the verbal memory components and naming capacity (from the BNT) and psychiatric self-assessment (from the HADS) as well as demographics (biological age, age at epilepsy onset and education) were examined. Finally, associations between test performance in the CDT and the RAVLT and the lateralization of left seizure onset were analysed. The correlation between presence of mesial sclerosis (yes/no; based on visual inspection) in the left temporal lobe and verbal memory deterioration (yes/no; based on 1 SD below the mean of the age- and education-related normative reference data) for both the CDT and the RAVLT were analysed.

Ethics

All the studies were approved by the Regional Ethical Review Board in Lund, Sweden.

Results

Summary of paper 1

The assumption was, mainly based on results on examination of handedness, that all patients in the study were left hemisphere dominant. For patients with right TLE, verbal memory was expected to be left-lateralized. However, three out of six patients showed right lateralized verbal memory (n=2) or verbal memory lateralized in both temporal lobes. For the patients with left TLE, all patients were expected to show left-lateralized verbal memory. Nevertheless, the expected pattern was seen only in five out of eight patients with left TLE. Two patients with left TLE showed bilateral verbal memory and one patient showed right-lateralized verbal memory. Hence, four patients demonstrated an unexpected verbal memory lateralization on fMRI. Two patients that suffered verbal memory deficits due to right TLR were identified as high-risk patients for verbal decline due to their bilateral language-dominance. Two patients that suffered verbal memory decline due to surgery could not be anticipated in advance, neither based on their RAS nor on their fMRI memory assessment.

Correlations between neuropsychological memory assessment and memory fMRI paradigms were seen for the visuospatial fMRI paradigm and the RCFT change score, indicating that strong left-lateralization for memory correlated with greater loss in non-verbal memory post-surgically. Also, for patients with right TLE, left verbal encoding correlated with better verbal outcome after surgery, while in left TLE, left-lateralization in verbal encoding correlated with worse verbal memory outcome.

In conclusion, paper 1 showed that fMRI language patterns are important indicators for post-surgical verbal memory decline in left TLE and right TLE, and that increased left lateralization in language regions, detected by fMRI, proposes higher risk for post left TLR memory decline. Memory fMRI did not add pre-surgical information on post-surgical risks on either an individual- or a group-level.

Summary of paper 2

There was no difference between the study group and the control group in terms of memory performance before the placement of hippocampal depth electrodes, in test session 1 (T1). At follow-up, in test session 2 (T2) (time elapsed from T1: 22 – 111 months, mean: 61.5 months), an equal proportion of patients in both groups had undergone right TLR (25 %), while the remaining patients had not undergone resective surgery. The study group performed significantly worse than the control group in four out of 12 memory variables (two variables for verbal learning; one variable for verbal recall; one variable for non-verbal memory). Most of the statistically non-significant differences between groups showed strong effect-sizes (>0.6), indicating that the small cohorts (n = 16 and 24) led to underpowered (= false-negative) statistical comparisons.

Memory scores worsened between the two test sessions in five out of six test variables in the study group. The same comparison for the control group showed a worsening in only two out of six memory variables. However, these differences were not statistically significant, something that might, at least in part, be explained by the fact that these comparisons were underpowered. Nonetheless, within-group changes in memory performance from T1 to T2 showed that the study group deteriorated by more than 20 % in verbal memory, while the control group showed only a 4 % deterioration.

Another important outcome parameter in this study was the individual change in memory performance equal to or exceeding 1 SD according to normative reference data. Such a change would be considered clinically significant in a routine setting. 56 % of the patients in the study group deteriorated in verbal memory performance while the corresponding decline in the control group was only 21 %.

Summary of paper 3

Out of the total cohort of 22 patients, results from five patients' 7T MRI segmentations were deselected due to technical difficulties, leaving a total of 17 7T MRI scans suitable for segmentation. In this group, significant correlations were found between hippocampal volumes and memory performance, where smaller volumes consistently corresponded with reduced memory performance. Bilateral hippocampal volume reduction (i.e. the sum of both the right and the left hippocampus) explained as much as 49 % of the total variance for verbal learning and 61 % of the total variance for verbal recall. A small volume of the total left hippocampus correlated with both verbal learning and recall. In addition, smaller volumes of several of the subregions of the left hippocampus correlated with

decreased verbal memory performance: the left CA1 correlated with decreased verbal learning and recall; the left CA2 with decreased verbal learning and verbal recall; the left CA3 with decreased verbal learning; the DG with decreased verbal learning. Also, smaller volumes of the left CA1 and DG correlated with deficits in non-verbal memory.

No correlations were found between the volume of the total right hippocampal and non-verbal memory nor between any of the right hippocampal subregions and any of the non-verbal memory variables. However, reduced total volume of the right hippocampus, as well small right CA1 and CA2 volumes, correlated with verbal memory performance.

A comparison between the visual 7T MRI inspections and memory performance was carried out for 21 patients (Table 1). One patient was deselected from this comparison due to non-applicable 7T scans.

Table 1.
Correspondence between 7T MRI visual inspection morphology and neuropsychology

Memory deficit	**Pathology L hippocampus**	**Pathology L TL (non-hippocampal)**	**Non-lesional**	**Pathology R TL**
Verbal memory, n = 15 (learning and recall: 9; learning 2; recall 4)	n = 2 (side of onset: L: 1; bilat: 1)	n = 3 (side of onset: L: 1; bilat: 2)	n = 9 (side of onset: L: 5; R: 2; bilat: 1; non-lat: 1)	n = 1 (side of onset: R:1)
Memory deficit	**Pathology R hippocampus**	**Pathology R TL (non-hippocampal)**	**Non-lesional**	**Pathology L TL**
Non-verbal memory, n = 18	n = 2 (side of onset: R: 2)	n = 1 (side of onset: bilat: 1)	n = 10 (side of onset: L: 4; R: 4; bilat: 1; non-lat: 1)	n = 5 (side of onset: L:2; ; bilat: 2; non-lat:1)

L = left; R = right; Bilat = bilateral; non-lat = non-lateralized; TL = temporal lobe;side of onset = seizure onset hemisphere defined by EEG-recordings (extracranial and/or intracranial) and semiology.

For 19 patients, comparisons between 3T and 7T MRI scans were performed. This was not the main scope of the study. However, this comparison showed additional pathology, not seen on 3T MRI, on the 7T MRI scans in one patient (bilateral minimal heterotopia).

Summary of paper 4

Two PCAs were performed, the first containing only verbal memory test variables and the second containing both verbal and non-verbal memory variables. The first PCA accounted for 81 % of the total variance and it revealed three components whereof one comprised learning and two comprised recall: (1) *verbal learning*, (2)

verbal long-term memory I, and (3) *verbal long-term memory II*. The second PCA accounted for 76 % of the total variance and it revealed four components whereof two comprised verbal memory and the remaining two non-verbal memory: (1) *verbal learning*, (2) *complex figural memory*, (3) *verbal retention*, and (4) *visuospatial memory*. Altogether, the PCAs showed coherence for the verbal learning variables of the CDT and the RAVLT, while divergence was seen for the recall variables of the two tests.

A Pearson's correlation analysis for memory components drawn from the first PCA showed that the RAVLT delayed recall variable was correlated to 80 % of the non-verbal memory measures, while neither the CDT learning nor recall variables were related to any of the non-verbal memory measures. Both the CDT and the RAVLT indicated clinically significant impairment of verbal memory (defined as performance ≥1 SD below the normative age- and education-related mean) in 70 - 80 % of patients with left TLE, with or without hippocampal sclerosis. The results demonstrate that the two tests do not differ with regard to concordance between detection of deficits and mesial sclerosis in left TLE. In addition, the analyses indicated that the RAVLT is correlated to nonverbal memory, something that was not seen for the CDT.

General discussion

The aim of this thesis was to evaluate the tools used in pre-surgical work-up for TLR to predict post-surgical memory outcome and to improve selection of patients eligible for TLR. Patient safety and the highest possible quality should be strived for, and that makes evaluation of all procedures and routines obligatory.

All the papers in this thesis focus on the accuracy, safety and potential of the instruments that we use in the pre-surgical work-up. All routines investigated in this thesis have proven valuable for epilepsy surgery. They all provide information on cerebral pathology and its functional correlates related to the patient's epilepsy. However, none of these methods has the potential to predict post-surgical verbal memory risks on its own. Instead, all methods must be seen in relation to each other and with consideration of the individual patient's medical history and present status.

Pre-surgical investigation – what can be expected?

What can be expected from surgery depends, not surprisingly, on what the physician wants to predict, and what the patient wants to know. To answer the question, many pieces in the puzzle must be found and put in the right place. In my thesis, I studied some of these pieces in an effort of seeing them in relation to one another, and in hoping to provide knowledge on how to improve patient selection and patient safety.

Memory assessment in the context of TLE and TLR

Neuropsychological examination, primarily memory testing, is to this day the most well-established routine for memory assessment prior to TLR (Vogt 2017). Testing of the function of the temporal lobe to-be-resected predicts which possible losses, in terms of memory function, the individual patient stands before. The neuropsychological assessment also estimates the patient's individual reserve-capacity, by assessing memory function in the contralateral hemisphere, and general cognitive ability [52,99]. Therefore, the appropriateness of the memory tests is essential. Another aspect is that if different tests are used for assessing memory prior to TLR these tests should evaluate memory concordantly. Most European centers for

epilepsy surgery use neuropsychological assessment for deciding on the appropriateness and the extent of the resection [63]. These assessments are based on estimates and experience with many different memory tests. In Europe, twelve different verbal memory tests and ten different non-verbal memory tests are currently being used for assessing declarative memory, respectively. In addition, several surgical centers also use neuropsychological test results for research purposes, e.g. for studying the effects of TLR and other surgical procedures on memory. The papers in this thesis used three different verbal memory tests and three different non-verbal memory tests. A prerequisite for research and for the comparison of findings from different centers is that the different tests used for assessment of the same cognitive abilities in fact do measure the same functions. As the present thesis shows, this is not always the case.

One study in my thesis (paper 4) investigated the coherence of two verbal memory tests (the CDT and the RAVLT) used for assessing memory prior to TLR. We found that the two tests only overlap in some of the memory measures (variables), but not in all. The memory variables that showed convergence were the ones representing verbal learning (encoding). Seemingly, verbal learning variables from memory tests are largely associated with short-term memory and only moderately with episodic long-term memory [100-102]. The two variables that have proven to more clearly measure declarative episodic memory, the recall variables from each respective test, did not converge in any of the analyses in the study. The main finding was that the RAVLT was significantly correlated to 80 % of the non-verbal memory variables while the CDT was not. This surprising finding might be explained by the fact that the RAVLT consists exclusively of concrete nouns, partly presented in an associative order (e.g. “school” followed by “parent” and “farmer” followed by “turkey”), while the CDT contains only 20 % nouns with remaining words being adjectives, verbs, pronouns, relative pronouns, conjunctions and adverbs. The words in the RAVLT thus allow for different mnemonic techniques, including non-verbal ones, which the CDT does to a much lesser extent. From a clinical perspective, that could mean that the RAVLT assesses memory function in a less “purely verbal” manner than the CDT does, potentially making the RAVLT less valid as a verbal memory test.

Another possible explanation for the differences in measuring recall might be the fact that the CDT and the RAVLT are based on slightly different prerequisites. In the RAVLT, the recall scores are based on the absolute number of words recalled 30 minutes after the encoding phase. In the CDT, the recall score is relative to how much (in percent) the patient remembers of his or her maximum performance during the encoding phase. In that sense, the CDT assesses the proportion of words lost over time (from encoding to recall), which the RAVLT does not. The notion that this could be of importance is highlighted in a paper by Helmstaedter and colleagues, showing that the only memory variable that differentiated patients with

left and right TLE was the loss of learnt words in delayed recall (in the German version of the RAVLT) [62]. The same group of researchers had earlier shown that this exact variable was suitable for differentiating left mesial from left neocortical lesions [101]. During the processing of the study data in study 4, this difference was acknowledged. We therefore created and analysed "loss of words" variables for both tests. In this analysis, the differences between the two tests remained.

The results from paper 4 highlight that verbal memory tests should not be seen as interchangeable. This information may have clinical consequences in terms of which test to use and to consider most reliable. At present, there is no indication which of the two tests better predicts verbal memory deficits prior to TLR, since a systematic follow-up on post-surgical memory deficits is not available. At least, both tests performed comparably in exhibiting verbal memory deficits in left mesial sclerosis.

For now, what could be hypothesized is the possible benefit from using both tests simultaneously in the clinic. As shown, the RAVLT represents more global aspects of memory, while the CDT is more stringently verbal in its composition. This indicates that these tests possess different structural characteristics. This notion might be useful in understanding the patient's individual functional adequacy versus reserve capacity relationship. For example, a normal performance in the RAVLT, not seen in the CDT, might indicate a good reserve capacity in the contralateral temporal lobe in left TLE, being a positive predictor for surgery. Thus, using both tests could bridge the space between verbal and non-verbal memory tests. This approach might also be helpful in planning for life after surgery with regard to compensatory strategies.

The relation between epilepsy, structural pathology and memory

Paper 1 investigated whether memory fMRI paradigms provide additional information on post-surgical memory outcome. The fMRI results were related to predictors for post-surgical memory outcome, namely pathology in the medial temporal lobe, language dominance and memory performance. The results from the study indicate that pre-surgical memory fMRI does not predict post-surgical memory deficits. However, the relationship between language activation, detected by fMRI during the verbal memory fMRI paradigm, does. Our main finding was that language activation detected by fMRI provided information that could potentially foresee post-surgical verbal memory loss after right TLR.

Even though the results from the memory fMRI paradigms in that paper did not predict post-surgical memory loss, they confirmed that verbal function and verbal memory are central and must not be overlooked in predicting memory deficits from TLR. These results had direct impact on the clinical routines in the epilepsy surgical

center at SUS in Lund: with few exceptions, patients to a much larger extent now undergo language fMRI, including those having surgery performed in the language-non-dominant temporal lobe and where there is no indication of atypical language lateralization (from neuropsychology, handedness, history of illness or presence of structural abnormalities).

In paper 2, the functional effects of structural damage *not* originating from the syndrome of TLE or from TLR, but instead from pre-surgical investigation, were studied. Invasive EEG is a routine procedure worldwide, but knowledge on its effects on memory is limited. The reoccurring question during clinical discussions of whether placement of longitudinal hippocampal depth electrodes for detection of seizure onset is potentially harmful for memory, was the starting point for this study. Initially, the discussion concerned mainly patients with non-affected memory performance at baseline (during the pre-surgical investigation). Gradually, the discussion covered all patients eligible for depth electrode investigation. Damage of already affected hippocampal and temporal lobe tissue may impose a worsening of memory functions. Simultaneously, it is not given that this invasive procedure leads to surgery and, thus, a chance of achieving seizure freedom. This can affect the risk-benefit evaluation.

All study patients had received hippocampal depth electrodes in their left temporal lobes, and all but one also in their right temporal lobe. This provided a chance for observing possible effects not only on verbal memory, but also on non-verbal memory. At baseline, the study- and the control groups did not differ with regard to memory performance, but at follow-up they did. The results provide support for verbal memory decline from depth electrodes, even after other factors with putative impact on memory were controlled for. The results for non-verbal memory were not as convincing, with only one non-verbal memory showing between-group differences at follow-up.

Although paper 2 was not a prospective study, the results raise a red flag concerning the use of longitudinal hippocampal depth electrodes. The method is no longer applied in the epilepsy surgery center in Lund. Instead, stereo-EEG or depth electrodes placed perpendicular to the hippocampus are used. This is not the case for many other centers, especially in the United States, where longitudinal depth electrodes are widely used. Until further evidence of the possible harmful effect of longitudinal depth electrodes on memory is available, the results from this study should be considered a warning.

Paper 3 confirmed different relations between variables of memory performance and hippocampal subregions [18,103-105]. These results have the potential to provide important information in the pre-surgical work-up for TLR. For example, the CA1 was strongly correlated to both verbal learning and recall. It has previously been reported that CA1 is the most affected hippocampal structure in terms of cell loss

[106]. If automated hippocampal volumetry, including segmentation, could be combined with visual structural inspection the results might be of importance, especially for the "non-lesional" patients. Such patients are usually considered less suitable, even non-eligible, for TLR. If volume loss in CA1 corresponds with deficits in memory, chances might be that they are presumed less as "high-risk patients" and that surgery can be an option.

Another interesting finding was that the coherence between verbal memory deficits and structural pathology in the left medial temporal lobe was sparse, only seen in approximately 50 % of patients with verbal memory deficits. About half of the patients with verbal memory deficits showed no left mesial temporal lobe pathology, and 15 % had pathology only in the right medial temporal lobe. Half of the patients in paper 3 with non-verbal memory deficits were in fact "non-lesional". Opposed to what was expected, only one fourth exhibited pathology in the right temporal lobe while one third exhibited pathology in the left temporal lobe. This discrepancy between side of pathology and corresponding memory deficits was also seen in the correlation between right subregional hippocampal volumes and memory. No correlation was seen between volumes of the right hippocampus and memory function, while left hippocampus volumes correlated with both verbal and non-verbal memory function. Whether this finding is caused by insufficient methods for investigating structural pathology, or if the answer can be found in the construction of the memory tests, or if it can be explained by atypical lateralization of language and memory in patients with TLE, cannot be answered by this thesis.

And what about the impact of language on memory function?

The results of this thesis raise many questions on the relationship between language and memory. For instance, one verbal memory test (the RAVLT) showed correlations to all the non-verbal memory variables. Both visual inspection of hippocampal pathology and the automated segmentation question the coherence between side of pathology (language-dominant or non-language-dominant) and deficits in verbal and non-verbal memory. In paper 2, longitudinal depth electrodes in the left hippocampus affected verbal memory, but this was not seen as distinctly for right hippocampal depth electrodes and non-verbal memory.

Paper 1 showed that fMRI can visualize the connections between language and verbal memory. This indicates that the prediction on "what can be expected from surgery" goes beyond the established concept of "functional adequacy" and "reserve capacity". This notion is further accentuated by the results from the left TLR group, which showed that a strong language lateralization in the anterior language regions seems to protect against memory decline from surgery. Since the theory of functional adequacy and reserve capacity is not based on language *per se* (even though the interrelationship between the both is well documented), knowledge on

language function and its cerebral distribution could add to the information on risk for memory deterioration after surgery.

Future perspectives

The study on the effects of hippocampal depth electrodes on memory has received strong reactions. It has been criticized for having methodological flaws, although I can't help to wonder whether the criticism comes from a place of *not* wanting to know if these results are true. Others have commended the study for its attempt to investigate the possible negative impact of depth electrodes [107], and one subsequently published clinical study has confirmed its results [108]. I hope that this discussion will lead to larger and prospective studies, which can confirm or refute the results from our study. Invasive EEG-monitoring is crucial in pre-surgical work-up for TLR and patients could be wrongfully excluded from surgery if they did not undergo invasive investigations. However, increasing knowledge on the safety of longitudinal electrodes and exploring alternative methods (such as e.g. stereo-EEG or conventional depth electrodes perpendicular to the longitudinal axis) is a part of the never-ending evolution of medicine: to secure the best possible and safest care of the patients.

My hope, based on the results from paper 3, is that hippocampal subregional volumetry becomes a supplementary diagnostic procedure for patients eligible for TLR. Future studies should also provide more information on the relation between memory deficits and volumes of hippocampal subregions.

I also look forward to fMRI becoming as much an unquestioned tool used for pre-surgical work-up for epilepsy surgery as structural MRI. By combining the display of neural activity *in vivo* with other methods for studying functional networks, e.g. the resting state network, additional information on TLE might be provided.

The results from paper 4 on memory tests have raised my attention toward the importance of critically reviewing the entire test battery used in patients with TLE and prior to TLR. Much is perhaps not unknown but unspoken when it comes to the methodological limitations and differences in the memory tests used for this purpose. It is highly important to evaluate the consistency of memory tests used simultaneously in pre-surgical and post-surgical evaluation for TLR. Also, a more active discussion regarding these issues is needed among neuropsychologists working with epilepsy surgery.

Conclusions

This thesis shows that no tool for predicting memory deficits from surgery can give the full picture of potential risks on its own.

The importance of MRI-confirmed pathology prior to TLR is indisputable. The information that MRI gives on hippocampal integrity can only be fully understood when combined with memory testing. And memory testing, combined with information on structural abnormalities, only tells half the story when the distribution of language is not displayed. One must always look to improve these tools and methods. Also, the aftermaths of our procedures must continuously and unconditionally be evaluated.

A final remark is that the risk of memory deficits from surgery cannot be measured in absolute terms. Assessing risks must always be done in the light of the individual patient. There will be risks that, seen from a physician's or neuropsychologist's point of view, are too high or unjustifiable. This work has opened my eyes for the fact that what is a risk for one patient and what might seem as a grey zone or a no-zone, can be justified in another case. In summary, what is undisputable is that in working with patients that suffer from all the difficulties related to TLE, or that undergo work-up for TLR, one must always question established clinical routines and continuously try to improve the investigational toolbox, to ensure the best possible quality and patient safety.

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References

1. Group GNDC. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurology.* 2017;16(11):877-897.
2. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology.* 2017;88(3):296-303.
3. Falco-Walter JJ, Scheffer IE, Fisher RS. The new definition and classification of seizures and epilepsy. *Epilepsy Res.* 2018;139:73-79.
4. Tatum WOt. Mesial temporal lobe epilepsy. *J Clin Neurophysiol.* 2012;29(5):356-365.
5. Curia G, Lucchi C, Vinet J, et al. Pathophysiogenesis of mesial temporal lobe epilepsy: is prevention of damage antiepileptogenic? *Curr Med Chem.* 2014;21(6):663-688.
6. Bien CG, Urbach H, Schramm J, et al. Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. *Neurology.* 2007;69(12):1236-1244.
7. Asadi-Pooya AA, Sperling MR. Age at onset in patients with medically refractory temporal lobe epilepsy and mesial temporal sclerosis: impact on clinical manifestations and postsurgical outcome. *Seizure.* 2015;30:42-45.
8. Villanueva V, Serratosa JM. Temporal lobe epilepsy: clinical semiology and age at onset. *Epileptic Disord.* 2005;7(2):83-90.
9. Hoppe C, Elger CE. Depression in epilepsy: a critical review from a clinical perspective. *Nat Rev Neurol.* 2011;7(8):462-472.
10. Steiger BK, Jokeit H. Why epilepsy challenges social life. *Seizure.* 2017;44:194-198.
11. Witt JA, Helmstaedter C. Cognition in epilepsy: current clinical issues of interest. *Curr Opin Neurol.* 2017;30(2):174-179.
12. Cheng D, Yan X, Gao Z, Xu K, Zhou X, Chen Q. Neurocognitive Profiles in Childhood Absence Epilepsy. *J Child Neurol.* 2017;32(1):46-52.

13. Hermann BP, Jones JE, Sheth R, et al. Growing up with epilepsy: a two-year investigation of cognitive development in children with new onset epilepsy. *Epilepsia.* 2008;49(11):1847-1858.

14. Reuner G, Kadish NE, Doering JH, Balke D, Schubert-Bast S. Attention and executive functions in the early course of pediatric epilepsy. *Epilepsy Behav.* 2016;60:42-49.

15. Hesdorffer DC, Hauser WA, Olafsson E, Ludvigsson P, Kjartansson O. Depression and suicide attempt as risk factors for incident unprovoked seizures. *Ann Neurol.* 2006;59(1):35-41.

16. Berg AT, Mathern GW, Bronen RA, et al. Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. *Brain.* 2009;132(Pt 10):2785-2797.

17. Salmenpera TM, Duncan JS. Imaging in epilepsy. *J Neurol Neurosurg Psychiatry.* 2005;76 Suppl 3:iii2-iii10.

18. Witt JA, Helmstaedter C, Elger CE. Is there evidence of a subordinate role of the hippocampal CA1 field for declarative memory formation? *Brain.* 2015;138(Pt 4):e343.

19. Ulate-Campos A, Fernandez IS. Cognitive and Behavioral Comorbidities: An Unwanted Effect of Antiepileptic Drugs in Children. *Semin Pediatr Neurol.* 2017;24(4):320-330.

20. Huang CW, Hayman-Abello B, Hayman-Abello S, Derry P, McLachlan RS. Subjective memory evaluation before and after temporal lobe epilepsy surgery. *PLoS One.* 2014;9(4):e93382.

21. Samarasekera SR, Helmstaedter C, Reuber M. Cognitive impairment in adults with epilepsy: The relationship between subjective and objective assessments of cognition. *Epilepsy Behav.* 2015;52(Pt A):9-13.

22. Amaral DG, Witter MP. The three-dimensional organization of the hippocampal formation: a review of anatomical data. *Neuroscience.* 1989;31(3):571-591.

23. Amaral DG, Scharfman HE, Lavenex P. The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies). *Prog Brain Res.* 2007;163:3-22.

24. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry.* 1957;20(1):11-21.

25. Matthews BR. Memory dysfunction. *Continuum (Minneap Minn).* 2015;21(3 Behavioral Neurology and Neuropsychiatry):613-626.

26. Thom M. Review: Hippocampal sclerosis in epilepsy: a neuropathology review. *Neuropathol Appl Neurobiol.* 2014;40(5):520-543.

27. Pauli E, Hildebrandt M, Romstock J, Stefan H, Blumcke I. Deficient memory acquisition in temporal lobe epilepsy is predicted by hippocampal granule cell loss. *Neurology.* 2006;67(8):1383-1389.

28. Witt JA, Coras R, Schramm J, et al. The overall pathological status of the left hippocampus determines preoperative verbal memory performance in left mesial temporal lobe epilepsy. *Hippocampus.* 2014;24(4):446-454.

29. Tulving E. Episodic and Semantic Memory. In: Bower GH, Donaldson W, Tulving E, États U, Office of Naval R, eds. *Organization of memory.* New York: Academic Press Inc; 1973:382-402.

30. Helmstaedter C, Grunwald T, Lehnertz K, Gleissner U, Elger CE. Differential involvement of left temporolateral and temporomesial structures in verbal declarative learning and memory: evidence from temporal lobe epilepsy. *Brain Cogn.* 1997;35(1):110-131.

31. Saling M, M, O'Shea MF, Weintrob DL, Wood AG, Reutens DC, Berkovic SF. Medial and lateral contributions to verbal memory: evidence from temporal lobe epilepsy. In: Yamadori A, Kawashima R, Fujii T, Suzuki K, eds. *Frontiers of memory.* Sendai: Tohoku University Press; 2002:151-158.

32. O'Kane G, Kensinger EA, Corkin S. Evidence for semantic learning in profound amnesia: an investigation with patient H.M. *Hippocampus.* 2004;14(4):417-425.

33. Helmstaedter C, Kockelmann E. Cognitive outcomes in patients with chronic temporal lobe epilepsy. *Epilepsia.* 2006;47 Suppl 2:96-98.

34. Hermann B, Seidenberg M. Epilepsy and cognition. *Epilepsy Curr.* 2007;7(1):1-6.

35. Jokeit H. Predicting verbal memory decline following anterior temporal lobectomy (ATL). *Neurology.* 2004;62(5):837;author reply 837.

36. Dabbs K, Jones J, Seidenberg M, Hermann B. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. *Epilepsy Behav.* 2009;15(4):445-451.

37. Helmstaedter C, Elger CE. The phantom of progressive dementia in epilepsy. *Lancet.* 1999;354(9196):2133-2134.

38. Helmstaedter C, Elger CE. Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease? *Brain.* 2009;132(Pt 10):2822-2830.

39. Mameniskiene R, Rimsiene J, Puronaite R. Cognitive changes in people with temporal lobe epilepsy over a 13-year period. *Epilepsy Behav.* 2016;63:89-97.

40. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med.* 2011;365(10):919-926.

41. Kwan P, Sperling MR. Refractory seizures: try additional antiepileptic drugs (after two have failed) or go directly to early surgery evaluation? *Epilepsia.* 2009;50 Suppl 8:57-62.

42. Brodie MJ. Pharmacological Treatment of Drug-Resistant Epilepsy in Adults: a Practical Guide. *Curr Neurol Neurosci Rep.* 2016;16(9):82.

43. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurol.* 2018;75(3):279-286.

44. Sillanpaa M, Anttinen A, Rinne JO, et al. Childhood-onset epilepsy five decades later. A prospective population-based cohort study. *Epilepsia.* 2015;56(11):1774-1783.

45. Baud MO, Perneger T, Racz A, et al. European trends in epilepsy surgery. *Neurology.* 2018;91(2):e96-e106.

46. Bjellvi J, Flink R, Rydenhag B, Malmgren K. Complications of epilepsy surgery in Sweden 1996-2010: a prospective, population-based study. *J Neurosurg.* 2015;122(3):519-525.

47. Baxendale S, Thompson PJ, Sander JW. Neuropsychological outcomes in epilepsy surgery patients with unilateral hippocampal sclerosis and good preoperative memory function. *Epilepsia.* 2013;54(9):e131-134.

48. Edelvik A, Rydenhag B, Olsson I, et al. Long-term outcomes of epilepsy surgery in Sweden: a national prospective and longitudinal study. *Neurology.* 2013;81(14):1244-1251.

49. Vakharia VN, Duncan JS, Witt JA, Elger CE, Staba R, Engel J, Jr. Getting the best outcomes from epilepsy surgery. *Ann Neurol.* 2018;83(4):676-690.

50. Spencer D, Burchiel K. Selective amygdalohippocampectomy. *Epilepsy Res Treat.* 2012;2012:382095.

51. Clusmann H, Schramm J, Kral T, et al. Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. *J Neurosurg.* 2002;97(5):1131-1141.

52. Baxendale S, Thompson PJ, Duncan JS. Neuropsychological function in patients who have had epilepsy surgery: a long-term follow-up. *Epilepsy Behav.* 2012;23(1):24-29.

53. Dulay MF, Busch RM. Prediction of neuropsychological outcome after resection of temporal and extratemporal seizure foci. *Neurosurg Focus.* 2012;32(3):E4.

54. Andersson-Roswall L, Engman E, Samuelsson H, Malmgren K. Cognitive outcome 10 years after temporal lobe epilepsy surgery: a prospective controlled study. *Neurology.* 2010;74(24):1977-1985.

55. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE. Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. *Ann Neurol.* 2003;54(4):425-432.

56. Helmstaedter C, Hauff M, Elger CE. Ecological validity of list-learning tests and self-reported memory in healthy individuals and those with temporal lobe epilepsy. *J Clin Exp Neuropsychol.* 1998;20(3):365-375.

57. Milner B. Psychological defects produced by temporal lobe excision. *Res Publ Assoc Res Nerv Ment Dis.* 1958;36:244-257.

58. Smith ML, Milner B. The role of the right hippocampus in the recall of spatial location. *Neuropsychologia.* 1981;19(6):781-793.

59. Saling MM. Verbal memory in mesial temporal lobe epilepsy: beyond material specificity. *Brain.* 2009;132(Pt 3):570-582.

60. Chelune GJ. Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. *Arch Clin Neuropsychol.* 1995;10(5):413-432.

61. Cheke LG, Clayton NS. Do different tests of episodic memory produce consistent results in human adults? *Learn Mem.* 2013;20(9):491-498.

62. Helmstaedter C, Wietzke J, Lutz MT. Unique and shared validity of the "Wechsler logical memory test", the "California verbal learning test", and the "verbal learning and memory test" in patients with epilepsy. *Epilepsy Res.* 2009;87(2-3):203-212.

63. Vogt VL, Aikia M, Del Barrio A, et al. Current standards of neuropsychological assessment in epilepsy surgery centers across Europe. *Epilepsia.* 2017;58(3):343-355.

64. Djordjevic J, Jones-Gotman M. Inquiry on assessments across epilepsy centers in different countries. In: Helmstaedter C, Hermann B, Lassonde M,

Kahane P, Arzimanoglou A, eds. *Neuropsychology in the care of people with epilepsy.* Paris: John Libbey Eurotext; 2011:13-26.

65. Hedegard E, Bjellvi J, Edelvik A, Rydenhag B, Flink R, Malmgren K. Complications to invasive epilepsy surgery workup with subdural and depth electrodes: a prospective population-based observational study. *J Neurol Neurosurg Psychiatry.* 2014;85(7):716-720.

66. Mormann F, Osterhage H, Andrzejak RG, et al. Independent delta/theta rhythms in the human hippocampus and entorhinal cortex. *Front Hum Neurosci.* 2008;2:3.

67. Wellmer J, Weber B, Urbach H, Reul J, Fernandez G, Elger CE. Cerebral lesions can impair fMRI-based language lateralization. *Epilepsia.* 2009;50(10):2213-2224.

68. Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res.* 2010;89(2-3):310-318.

69. Witt JA, Coras R, Schramm J, et al. Relevance of hippocampal integrity for memory outcome after surgical treatment of mesial temporal lobe epilepsy. *J Neurol.* 2015;262(10):2214-2224.

70. Baxendale S, Thompson P, Harkness W, Duncan J. Predicting memory decline following epilepsy surgery: a multivariate approach. *Epilepsia.* 2006;47(11):1887-1894.

71. Duncan JS. Imaging in the surgical treatment of epilepsy. *Nat Rev Neurol.* 2010;6(10):537-550.

72. Breyer T, Wanke I, Maderwald S, et al. Imaging of patients with hippocampal sclerosis at 7 Tesla: initial results. *Acad Radiol.* 2010;17(4):421-426.

73. Colon AJ, Osch M, Buijs M, et al. MEG-guided analysis of 7T-MRI in patients with epilepsy. *Seizure.* 2018;60:29-38.

74. Zentner J, Hufnagel A, Wolf HK, et al. Surgical treatment of temporal lobe epilepsy: clinical, radiological, and histopathological findings in 178 patients. *J Neurol Neurosurg Psychiatry.* 1995;58(6):666-673.

75. Kasasbeh A, Hwang EC, Steger-May K, et al. Association of magnetic resonance imaging identification of mesial temporal sclerosis with pathological diagnosis and surgical outcomes in children following epilepsy surgery. *J Neurosurg Pediatr.* 2012;9(5):552-561.

76. Powell HW, Parker GJ, Alexander DC, et al. Abnormalities of language networks in temporal lobe epilepsy. *Neuroimage.* 2007;36(1):209-221.

77. Hamberger MJ, Cole J. Language organization and reorganization in epilepsy. *Neuropsychol Rev.* 2011;21(3):240-251.

78. Binder JR, Swanson SJ, Hammeke TA, et al. Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology.* 1996;46(4):978-984.

79. Rutten GJ, Ramsey NF, van Rijen PC, Alpherts WC, van Veelen CW. FMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. *Neuroimage.* 2002;17(1):447-460.

80. Woermann FG, Jokeit H, Luerding R, et al. Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology.* 2003;61(5):699-701.

81. Janszky J, Jokeit H, Kontopoulou K, et al. Functional MRI predicts memory performance after right mesiotemporal epilepsy surgery. *Epilepsia.* 2005;46(2):244-250.

82. Avila C, Barros-Loscertales A, Forn C, et al. Memory lateralization with 2 functional MR imaging tasks in patients with lesions in the temporal lobe. *AJNR Am J Neuroradiol.* 2006;27(3):498-503.

83. Strandberg M, Elfgren C, Mannfolk P, et al. fMRI memory assessment in healthy subjects: a new approach to view lateralization data at an individual level. *Brain Imaging Behav.* 2011;5(1):1-11.

84. Petersson KM, Sandblom J, Elfgren C, Ingvar M. Instruction-specific brain activations during episodic encoding. a generalized level of processing effect. *Neuroimage.* 2003;20(3):1795-1810.

85. Roland PE, Eriksson L, Stone-Elander S, Widen L. Does mental activity change the oxidative metabolism of the brain? *J Neurosci.* 1987;7(8):2373-2389.

86. Ljung H, Strandberg MC, Bjorkman-Burtscher IM, Psouni E, Kallen K. Test-specific differences in verbal memory assessments used prior to surgery in temporal lobe epilepsy. *Epilepsy Behav.* 2018;87:18-24.

87. Yushkevich PA, Pluta JB, Wang H, et al. Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. *Hum Brain Mapp.* 2015;36(1):258-287.

88. Wisse LE, Kuijf HJ, Honingh AM, et al. Automated Hippocampal Subfield Segmentation at 7T MRI. *AJNR Am J Neuroradiol.* 2016;37(6):1050-1057.

89. Claeson LE, Esbjörnsson E, Carlé BM, Wahlbin M. *Claeson-Dahls test för inlärning och minne. Reviderad version: Håkan Nyman.* Stockholm: Hogrefe Psykologiförlaget AB; 1998.

90. Lezak MD, Howieson DB, Bigler ED, D. T. Memory II: Batteries, Paired Memory Tests, and Questionnaires. In: *Neuropsychological Assessment.* New York: Oxford University Press; 2012:522-541.

91. Loring DW, Strauss E, Hermann BP, et al. Differential neuropsychological test sensitivity to left temporal lobe epilepsy. *J Int Neuropsychol Soc.* 2008;14(3):394-400.

92. Bell BD. WMS-III Logical Memory performance after a two-week delay in temporal lobe epilepsy and control groups. *J Clin Exp Neuropsychol.* 2006;28(8):1435-1443.

93. Strauss E, Sherman E, Spreen O. Memory. In: *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary.* 3 ed. New York: Oxford University Press; 2006:678-890.

94. Kneebone AC, Lee GP, Wade LT, Loring DW. Rey Complex Figure: figural and spatial memory before and after temporal lobectomy for intractable epilepsy. *J Int Neuropsychol Soc.* 2007;13(4):664-671.

95. Barr W, Morrison C, Zaroff C, Devinsky O. Use of the Brief Visuospatial Memory Test-Revised (BVMT-R) in neuropsychological evaluation of epilepsy surgery candidates. *Epilepsy Behav.* 2004;5(2):175-179.

96. Vaz SA. Nonverbal memory functioning following right anterior temporal lobectomy: a meta-analytic review. *Seizure.* 2004;13(7):446-452.

97. Strauss E, Sherman E, Spreen O. Language Tests. In: *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary.* 3 ed. New York: Oxford University Press; 2006:891-962.

98. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.

99. Baxendale S, Thompson P. Red flags in epilepsy surgery: Identifying the patients who pay a high cognitive price for an unsuccessful surgical outcome. *Epilepsy Behav.* 2018;78:269-272.

100. Gavett BE, Horwitz JE. Immediate list recall as a measure of short-term episodic memory: insights from the serial position effect and item response theory. *Arch Clin Neuropsychol.* 2012;27(2):125-135.

101. Hermann BP, Seidenberg M, Schoenfeld J, Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Arch Neurol.* 1997;54(4):369-376.

102. Jonides J, Lewis RL, Nee DE, Lustig CA, Berman MG, Moore KS. The mind and brain of short-term memory. *Annu Rev Psychol.* 2008;59:193-224.

103. Travis SG, Huang Y, Fujiwara E, et al. High field structural MRI reveals specific episodic memory correlates in the subfields of the hippocampus. *Neuropsychologia.* 2014;53:233-245.

104. Mueller SG, Laxer KD, Scanlon C, et al. Different structural correlates for verbal memory impairment in temporal lobe epilepsy with and without mesial temporal lobe sclerosis. *Hum Brain Mapp.* 2012;33(2):489-499.

105. Baxendale SA, Van Paesschen W, Thompson PJ, Duncan JS, Harkness WF, Shorvon SD. Hippocampal cell loss and gliosis: relationship to preoperative and postoperative memory function. *Neuropsychiatry Neuropsychol Behav Neurol.* 1998;11(1):12-21.

106. Blumcke I. Neuropathology of focal epilepsies: a critical review. *Epilepsy Behav.* 2009;15(1):34-39.

107. Drane DL, Gross RE. Hippocampal Depth Electrodes in Epilepsy Surgery: Diagnostic or Damaging? *Epilepsy Curr.* 2018;18(2):104-106.

108. Helmstaedter C, Gielen GH, Witt JA. The immediate and short-term effects of bilateral intrahippocampal depth electrodes on verbal memory. *Epilepsia.* 2018;59(6):e78-e84.

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