Cognitive, emotional and psychosocial functions after resective epilepsy surgery

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In memory of my beloved mother

ABSTRACT

Epilepsy surgery is a potentially curing treatment for a selected group of patients with drug-resistant focal epilepsy. Cognitive side-effects after temporal lobe resections (TLR) are well documented but it is still difficult to predict individual memory outcome after TLR. Concerning frontal lobe resections (FLR), fewer studies have addressed the cognitive outcome. The aim of this thesis was to develop a prediction model for verbal memory decline after TLR and to further the knowledge of cognitive, emotional and psychosocial outcome after FLR for epilepsy.

In Study I, regression analyses based on pre- and postoperative cognitive data from 110 patients who underwent TLR for epilepsy were made to develop a prediction model for verbal memory decline after TLR. In Study II, cognitive outcome two years after FLR for epilepsy was studied through analyses of neuropsychological data from 30 consecutive FLR patients. Study III was an interview study including 14 FLR patients and 12 of their respective relatives who were interviewed about experiences of emotional, cognitive and psychosocial consequences of FLR. Data were analyzed by qualitative content analysis. In Study IV, decision making after FLR was explored using the Iowa Gambling Task (IGT). The same 14 FLR patients as in Study III were included.

Results from study I identified left sided surgery, inclusion of hippocampus in the resection, high preoperative verbal memory function and a history of tonic-clonic seizures (TCS) as predictors of significant memory decline after TLR. The results from study II mainly showed cognitive stability two years after FLR. However, at the individual level 44% of patients had reliable decline in a verbal reasoning task. In study III, patients and relatives described positive experiences after FLR, like increased autonomy and more joy in life, but also negative ones, such as loss of energy and social withdrawal. Study IV showed that patients had problems with decision making after FLR. This was demonstrated through a failure to learn from feedback throughout the IGT.

To conclude, this thesis has contributed with a prediction model which included four clinically useful predictors of memory decline after TLR. The FLR studies demonstrated mainly cognitive stability over time, positive as well as negative individual experiences of cognitive, emotional and psychosocial functions and difficulties associated with decision making. These contributions will be valuable to share with patients and their families in the preoperative counselling process preceding a decision about TLR or FLR.

Keywords: epilepsy, epilepsy surgery, frontal lobe resection, temporal lobe resection, neuropsychology, cognitive outcome, verbal memory decline, executive functions, decision making, penalized regression analysis, qualitative content analysis

SAMMANFATTNING

Epilepsi är en av de vanligaste kroniska neurologiska sjukdomarna och orsakar såväl stort personligt lidande som negativa samhällsekonomiska konsekvenser när individer på grund av epileptiska anfall och kognitiva funktionsnedsättningar ställs utanför arbetsmarknaden. Omkring två tredjedelar av personer med epilepsi blir anfallsfria med läkemedelsbehandling medan den resterande tredjedelen fortsätter att ha anfall och de brukar då benämnas som läkemedelsrefraktära. En liten andel av dessa individer kan komma ifråga för neurokirurgisk behandling. En sådan går i de flesta fall till så att anfallsgenererande hjärnvävnad identifieras och avlägsnas vilket kan leda till anfallsfrihet. Omkring 50% av de som opereras är bestående anfallsfria. Den vanligaste typen av epilepsioperation är en tinninglobsresektion (TLR) där delar av tinningloben avlägsnas. Denna typ av operation har goda resultat med omkring 50% bestående anfallsfrihet, dock är en vanlig sidoeffekt minnesförsämring då de strukturer som avlägsnas är centrala för inlärningsförmåga och minnesfunktioner. Den näst vanligaste operationstypen är frontallobsresektion (FLR) där delar av frontalloben (pannloben) på motsvarande sätt avlägsnas. Denna typ av operation ger anfallsfrihet i något lägre grad än efter TLR. Konsekvenserna av FLR, för kognitiva, känslomässiga och psykosociala funktioner är betydligt mindre studerade än vid TLR.

Inför en eventuell operation går patienterna igenom omfattande utredningar i syfte att identifiera anfallsgenererande hjärnvävnad, bedöma risker med operation och samla information om kognitiva funktioner och psykiskt mående för att hjälpa patienten och de närstående att på ett välavvägt sätt kunna fatta ett beslut om operation. I denna utredning ingår neuropsykologisk bedömning där patienten genomgår kognitiva tester i syfte att kartlägga nuvarande funktionsnivå samt om möjligt kunna förutsäga hur densamma kan komma att påverkas av operationen. Medicinska utredningar som genomförs är bland annat magnetkameraundersökning av hjärnan för att identifiera

eventuella strukturella skador som skulle kunna orsaka epilepsi och anfallsutredning med elektroencefalografi (EEG) samtidigt med videoregistrering av kliniska symtom – s k video-EEG i syfte att avläsa elektrisk aktivitet från hjärnan som kan indikera anfall eller bakomliggande epilepsirelaterad aktivitet. Det epilepsikirurgiska teamet som genomför dessa utredningar ansvarar sedan för att göra en samlad bedömning avseende den enskilda patientens möjligheter till anfallsfrihet eller -lindring samt att i rådgivningen riktad till patienten väga dessa emot möjliga risker och eventuella förväntade funktionsförsämringar.

Denna avhandling bygger på fyra studier som syftar till att öka kunskapen om individens kognitiva, känslomässiga och sociala förmågor efter epilepsikirurgi.

Studie I syftade till att skapa en statistisk modell för att på individnivå kunna förutsäga risk för försämring av språkliga inlärnings- och minnesfunktioner efter TLR. Tidigare forskning har visat att omkring 20 - 40% av individer som genomgår en TLR försämras i sitt språkliga minne men att skillnaderna avseende individuell försämring är stora och att det kan vara svårt att förutse vilka individer som kommer att drabbas mest. Modellen som togs fram i denna studie identifierade fyra faktorer som bidrog påtagligt till försämring i språkliga minnesförmågor efter TLR. Risken var störst hos de individer som gjort en operation i vänster hjärnhalva och där operationen inkluderat strukturen hippocampus. De individer som hade en god språklig minnesförmåga före operationen och som hade haft tonisk-kloniska anfall, en sorts anfall som involverar ett större område av hjärnvävnaden i det epileptiska anfallet, löpte också större risk att drabbas av försämrade minnesförmågor. Modellen identifierade 82% av de individer som i materialet hade drabbats av språklig minnesförsämring och kommer att kunna användas i rådgivningen inför TLR.

De tre resterande studierna syftade till att öka kunskapen om neuropsykologiska effekter av frontallobsresektioner.

I **studie II** analyserades neuropsykologiska data insamlade före samt två år efter FLR hos 30 individer och jämfördes med data från 25 friska kontrollpersoner. Huvudresultatet visade att den absoluta majoriteten av de personer som genomgått FLR hade oförändrad kognitiv funktionsnivå vilket i sammanhanget får anses vara ett positivt resultat då det skulle innebära att man kan genomgå den aktuella operationen utan någon större risk för försämrad kognition. Vid närmare analys av resultat på individnivå framkom dock att en relativt hög andel (44%) av patienterna uppvisade försämrade resultat avseende en uppgift som syftar till att mäta språkligt resonerande. Dessa försämringar sågs dock bara vid operationer i vissa delar av frontalloben.

Studie III var en kvalitativ studie där 14 patienter som genomgått FLR och 12 av deras närstående intervjuades. Syftet var att undersöka hur patienter och närstående upplever kognitiva, känslomässiga och psykosociala förmågor efter FLR. Positiva upplevelser av ökad autonomi, bättre tillgång till känslolivet och förmåga att uppleva välbehag framkom, och var huvudsakligen relaterat till anfallsfrihet. Negativa erfarenheter i form av ökad trötthet och social tillbakadragenhet med nedstämdhet och minskad lust i förhållande till saker man tidigare uppskattat framkom också. Detta beskrevs som svårt att förhålla sig till, såväl för patienterna själva som för deras närstående. Det varierade hur patienterna tänkte kring sin förändrade funktionsnivå och dess bakomliggande orsaker. En del spekulerade i att såväl åldrande som läkemedelsbiverkningar kunde påverka energinivån negativt medan andra var tämligen säkra på att det var operationen som orsakat mental trötthet. Totalt sett beskrev dock såväl patienter som närstående att det varit väl värt risken att genomgå operationen och att de positiva konsekvenserna var övervägande.

Studie IV syftade till att utforska förmågan till beslutsfattande hos patienter som genomgått FLR. Samma 14 patienter som ingick i studie

III undersöktes och deras resultat jämfördes med 30 friska kontrollpersoner på ett test som avser att mäta beslutsfattande baserat på emotionell återkoppling. Resultat visade att de individer som genomgått FLR hade svårare att lära sig från den återkoppling testet gav dem över tid vilket resulterade i sämre beslutsfattande mot slutet av testet jämfört med kontrollgruppen. Kontrollpersonerna blev tvärtom allt bättre under testets gång på att förstå hur de skulle göra för att lyckas. Sämre beslutsfattande sågs i viss mån höra ihop med lägre resultat i uppgifter som krävde arbetsminne och impulskontroll vilket kan vara en del av förklaringen till ett sämre utfall i patientgruppen. Resultat från denna studie, som är den första att undersöka beslutsfattande vid FLR, bör prövas i framtiden med ett större antal deltagare för att värdera dess generaliserbarhet.

Sammanfattningsvis har denna avhandling kunnat identifiera fyra kliniska variabler som prediktorer för språklig minnesförsämring efter TLR; operation i vänster hjärnhalva, strukturen hippocampus inkluderad i operationen, god preoperativ språklig minnesförmåga och förekomst av tonisk-kloniska anfall före operationen. Prediktionsmodellen kommer att kunna användas i klinisk rådgivning inför beslut om epilepsikirurgi och ge individen bättre förutsättningar att fatta ett välavvägt beslut om operation eller ej. Avhandlingen har också kunnat visa att individer två år efter FLR huvudsakligen har stabil kognitiv funktionsnivå vilket är viktig information att kunna delge de individer som står inför ett beslut om FLR. Resultaten från intervjustudien utgör ett underlag för att diskutera psykologiska och sociala konsekvenser med såväl patienter som närstående i samband med FLR under preoperativ rådgivning men också som en utgångspunkt för kartläggning vad gäller behov av stödinsatser och rehabiliterande åtgärder efter operationen. I detta sammanhang kan även konsekvenser av påvisade svårigheter vad gäller beslutsfattande vara värdefullt att uppmärksamma och utforska vidare i dialog med patienter och familjer.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Ljunggren, S*., Andersson-Roswall, L*., Imberg, H., Samuelsson, H., & Malmgren, K. Predicting verbal memory decline following temporal lobe resection for epilepsy. *Acta Neurol Scand.* 2019; 140(5): 312-319.

II. Ljunggren, S., Andersson-Roswall, L., Rydenhag, B., Samuelsson, H., & Malmgren, K. Cognitive outcome two years after frontal lobe resection for epilepsy - a prospective longitudinal study. *Seizure*. 2015; 30: 50-56.

III. Ljunggren, S., Winblad, S., Hallgren Graneheim U., Malmgren, K. & Ozanne, A. Experiences of emotional and psychosocial functioning after frontal lobe resection for epilepsy. *Epilepsy Behav.* 2021;121(Pt A):108077.

IV. Ljunggren, S., Winblad, S., Samuelsson, H. & Malmgren, K. Decision making after frontal lobe resection for epilepsy. *Manuscript.*

* equal contributions

CONTENTS

ABBREVIATIONS

AED	Antiepileptic Drug
AUC	Area Under the Curve
CD	Claeson-Dahl learning and retention test
CDDR	Claeson-Dahl Delayed Recall
CDWS	Claeson-Dahl Weighted Sum
CI	Confidence Interval
CM	Cronholm-Molander memory test
CMIR	Cronholm-Molander Immediate Recall
CWFT	Chicago Word Fluency Task
COWAT	Controlled Oral Word Association Task
D-KEFS	Delis-Kaplan Executive Function System
DR	Delayed Recall
EEG	Electroencephalography
EF	Executive Functions
EpiCARE	European Reference Network for rare and complex epilepsies
FLE	Frontal Lobe Epilepsy
FLR	Frontal Lobe Resection
fMRI	Functional Magnetic Resonance Imaging
FrSBe	Frontal Systems Behavior Scale

FSIQ	Full Scale IQ
HADS	Hospital Anxiety and Depression Scale
HRQOL	Health-Related Quality Of Life
HS	Hippocampal Sclerosis
IGT	Iowa Gambling Task
ILAE	International League Against Epilepsy
IR	Immediate Recall
IQ	Intelligence Quotient
MEG	Magnetencephalography
MFS	Mental Fatigue Scale
MRI	Magnetic Resonance Imaging
MST	Multiple Subpial Transections
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PIQ	Performance IQ
POI	Perceptual Organization Index
PSI	Processing Speed Index
PWE	People With Epilepsy
RCI	Reliable Change Indices
ROCF	Rey-Osterrieth Complex Figure test

QCA	Qualitative Content Analysis
SMA	Supplementary Motor Area
SNESUR	Swedish National Epilepsy Surgery Register
TCS	Tonic-Clonic Seizure
TLE	Temporal Lobe Epilepsy
TLR	Temporal Lobe Resection
TMT	Trail Making Test
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
VCI	Verbal Comprehension Index
VIQ	Verbal IQ
VNS	Vagus Nerve Stimulation
WAIS	Wechsler Adult Intelligence Scale
WMI	Working Memory Index
WS	Weighted Sum

1 INTRODUCTION

1.1 EPILEPSY

According to the definition of 2005 by the International League Against Epilepsy (ILAE), epilepsy is "*a disease of the brain characterized by an enduring disposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition*".[1] It is one of the most common neurological disorders with a prevalence around 0.7%[2, 3] and affects around 50 million people worldwide.[4] As the definition implies, individuals with epilepsy often suffer from more than just the seizures as epilepsy is associated with cognitive dysfunction, psychiatric comorbidity, work related problems and social stigma.[1, 5-7]

Classification of seizures

An epileptic seizure is defined as *"a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain"*.[1] According to the most recent classification, seizures are defined according to their etiology as either focal, generalized or unknown.[8] Focal seizures have a localized seizure onset with support from clinical and/or EEG findings. Generalized seizures affect both hemispheres at seizure onset according to both behavior and EEG findings. A seizure classified as unknown refers to a situation where the onset is unknown but other manifestations of seizures are present.[8]

Focal seizures are further classified as either *aware* or with *impaired awareness*, referring to the patients' level of awareness during the seizure. The next level describes the onset as *motor* or *non-motor* where presence of motor symptoms is considered. Focal aware as well as focal seizures with impaired awareness can further develop into *tonic-clonic seizures* and are then denoted *focal to bilateral tonic-clonic seizures*. Generalized seizures are classified as either *motor* or *non-motor* (absence) seizures.[8]

Temporal lobe epilepsy

The most common form of focal epilepsy is temporal lobe epilepsy (TLE).[9] Seizures typically start with an aura which often includes emotions of fear or anxiety or epigastric rising sensation. The aura is often followed by a period of impaired awareness where the person is unresponsive and performs repetitive purposeless actions, so called automatisms. The seizure usually lasts around two minutes, headache and postictal tiredness are common. TLE is a rather homogeneous condition where most seizures stem from the medial temporal lobe and are often associated to some kind of cerebral injury during infancy or childhood, for example febrile seizures or perinatal injuries.[9, 10]

Frontal lobe epilepsy

The second most common type of focal epilepsy is frontal lobe epilepsy (FLE).[11] These seizures are often shorter in duration but more frequent than temporal lobe seizures and are more often nocturnal. They are more heterogeneous in expression, depending on which part of the frontal lobes they originate from. For example, seizures starting in motor cortex often lead to clonic jerks. Awareness is most often preserved. Frontal lobe seizures with impaired awareness can include complex automatisms and vocalizing (involuntarily sounding) and are often socially disabling. To conclude, frontal lobe seizures reflect the large heterogeneity of the frontal lobes and etiologies vary from for example cortical malformations and tumors to hemangiomas and focal cortical dysplasia.[12, 13]

Treatment

Antiepileptic drug (AED) treatment is a symptomatic treatment, reducing the risk for epileptic seizures. During the first years of disease, AED treatment is tried out with the goal to achieve seizure freedom. If this is not reached with the first drug, others are tested. Approximately two thirds of people with epilepsy (PWE) get seizure free on medical treatment while the remaining third continue to have seizures.[14] The ILAE has defined drug-resistant epilepsy as the failure of at least two adequate trials of tolerated AED schedules.[14] These patients should be referred to a tertiary referral centre for evaluation of the diagnosis and treatment options. If the diagnosis of focal epilepsy is correct, epilepsy surgery might be one of the treatment alternatives. Otherwise, investigations can lead to treatment with, for instance, Vagus Nerve Stimulation (VNS), ketogenic diet, or immunotherapy if the focal seizures are considered to be caused by autoimmune encephalitis.[15]

1.2 EPILEPSY AND NEUROPSYCHOLOGY

Prevalence of cognitive deficits is high in PWE and psychiatric comorbidity is common, mostly depression and anxiety.[16-18] Several factors can influence cognitive functions in PWE including fixed factors such as type of etiology, localization and lateralization of etiology, age at epilepsy onset and general intellectual functions. Fluid factors like AED effects, seizure frequency, interictal EEG-abnormalities and mood can also influence cognition and achievement on neuropsychological tests.[19, 20] There is an increased knowledge that the prevalence of cognitive deficits is high already in newly diagnosed epilepsy, which challenges the previous assumption that seizures *per se* lead to cognitive decline. Studies show that about 70% of people with new-onset epilepsy demonstrate cognitive and/or behavioral symptoms of clinical importance even before treatment is started.[21-23] The recent view on cognitive deficits in epilepsy is that they may be the result of the same pathological process that generates seizures[24] and thereby closely linked to the etiology of the epilepsy.

A bidirectional relationship between epilepsy and mood or anxiety disorder has recently been increasingly emphasized.[25] A lifetime prevalence of 35% regarding psychiatric disorders in PWE (compared to a prevalence of 20% for controls) has been identified in population-based studies, where mood and anxiety disorders are the most frequent in adults.[7] Depression has been shown to double the risk of developing epilepsy[26] and the prevalence of depression in newly diagnosed epilepsy varies from 11% to 44.7%.[27-29] In a recent study, the prevalence of anxiety at the time of epilepsy diagnosis was around 35%.[29] The risk of psychiatric comorbidities is even higher (up to four times) in drug-resistant epilepsy.[30] The increasing number of studies indicating the bilateral relationship show that there are shared pathological mechanisms between epilepsy, anxiety and depression.[25]

Cognition in temporal lobe epilepsy

Memory dysfunction is strongly associated with temporal lobe epilepsy (TLE) where structures in the medial temporal lobe essential for learning and memory are affected.[31] Hippocampus is a structure in the limbic system and the medial temporal lobe. It is often involved in seizure onset. Around 80% of the patients with TLE have seizures originating from one or both hippocampi.[9] TLE is often associated with various degrees of cell loss in the hippocampus; hippocampal sclerosis (HS), which is related to memory impairment.[31] Memory problems in TLE with HS are reported to accelerate over time and the condition is potentially associated with neurodegenerative processes.[32, 33] Some studies also indicate deficits in executive functions (EF) in TLE, but there is no consensus regarding which aspects of EF that are impaired and to what extent.[34, 35]

Cognition in frontal lobe epilepsy

Even though frontal lobe epilepsy (FLE) is the second most common focal epilepsy, constituting around 20-30 % of focal epilepsies[11], there are few neuropsychological studies regarding cognitive functions. Attempts to define a specific cognitive profile in FLE have been made but studies have been mostly conducted on small and heterogeneous samples precluding firm conclusions.[36-39] Deficits in speed/attention, phonological processing, planning, working memory, motor coordination, response maintenance and inhibition capacity have been described in some studies.[36, 40, 41] Other studies found impairments in cost estimates tasks, tasks requiring divided attention and set shifting, with the largest impairments in patients with seizure onset in the left frontal lobe.[42-46] The majority of neuropsychological measures have not been able to either lateralize or localize specific deficits related to FLE.[36, 37, 42, 47] A recent meta-analysis concluded that there are general cognitive deficits associated with FLE in both adults and children, including working memory, executive functions and problem solving while adults also demonstrate deficits in concept formation and verbal comprehension.[39] The authors commented on the fact that studies are heterogeneous which precludes in-depth studies on FLE. Memory functions have been studied and impairments are reported in long-term memory but not to the same extent as in TLE.[41, 48] Social cognition has been the focus of a limited number of studies on FLE.[49-51] The results indicated that patients had problems with humor appreciation, facial emotion recognition, empathy and Theory of Mind (the ability to attribute mental states to ourselves and others).[52]

1.3 EPILEPSY SURGERY

Epilepsy surgery is an evidence-based neurosurgical treatment option for selected patients with drug-resistant epilepsy.[53-55] Around 50 patients (both children and adults) undergo epilepsy surgery in Sweden every year according to the Swedish National Epilepsy Surgery Register (SNESUR) which collects prospectively reported data from the six Swedish epilepsy surgery centres. For adult patients, the mean age at surgery is around 30 years of age and the mean duration of epilepsy at surgery is around 15 years. While temporal lobe resection (TLR) has been the overwhelmingly most common epilepsy surgery procedure for a long time, this has changed during the last decade, but TLR still represents almost 50% of the procedures in Sweden according to data from SNESUR. For the majority of cases, TLR is a standardized procedure including a unilateral resection of the hippocampus and most often the amygdala but sparing more of the lateral temporal lobe.[56] The second most common procedure is a frontal lobe resection (FLR)[57], in recent years performed in around 23% of the patients. These resections are individually tailored according to findings from the presurgical investigations.[58] The basic work-up includes magnetic resonance imaging (MRI) of the brain with special epilepsy sequences, long-term seizure recording with video-EEG, clinical neurological examination and neuropsychological assessment.[59] At Sahlgrenska University Hospital all presurgical candidates undergo a functional MRI (fMRI) regarding language lateralization before decision is made about resective epilepsy surgery. In cases where for example MRI is negative (no visible pathology related to the epilepsy onset) further investigations are necessary, such as positron emission tomography (PET) or magnetencephalography (MEG) to provide more information in order to plan seizure recording with implanted depth electrodes.[60, 61] Findings from the work-up are repeatedly discussed in a multidisciplinary team conference and the patients' chances of seizure-freedom or -reduction are weighted against the risk of complications or expected adverse events.[55, 62, 63] Long-term follow-up studies show that 40-50% of the patients have been continuously free from seizures with impaired awareness ten years after resective epilepsy surgery.[64, 65] The most favorable outcomes, about 80% seizure freedom, are seen in resections of well-defined epileptogenic lesions, such as low-grade tumors and cavernomas.[66]

The role of neuropsychology in epilepsy surgery

While neuropsychological assessment has been a part of the presurgical workup in epilepsy surgery for many decades[67], its' role has partly changed from being strictly oriented towards localization and lateralization of seizure focus into becoming more complex and collaborative in nature.[20, 68] The ILAE Neuropsychology Task Force has recently listed four key purposes of the presurgical neuropsychological assessment.[69, 70] These are listed below:

1. Establish a baseline against which change can be measured following surgery.
2. Provide a collaborative contribution to seizure characterization, lateralization and localization.
3. Provide evidence-based predictions of cognitive risk associated with the proposed surgery.
4. Provide the evidence base for comprehensive preoperative counselling, including exploration of patient expectations of surgical treatment.

The neuropsychological assessment should encompass both objective test findings, subjective experiences of cognitive functions, screening for psychiatric comorbidities and patient expectations on surgery. To include subjective experiences is emphasized since research has shown a poor correlation between formal test findings and subjective memory complaints.[71] It is also stressed that the assessment must be up to date (<18 months old for adult patients) and should include assessment of many different cognitive domains as well as measures of psychosocial function and health-related quality of life (HRQOL).[70] This emphasizes that the results on cognitive tests must be interpreted within a wider framework, including psychiatric health, impact from epilepsy specific variables such as proximity to latest seizure, current AED and EEG findings.[19] The assessment should be used to predict the likely cognitive outcomes after surgery and to evaluate cognitive reserve capacity with which potential declines could be managed.

Cognitive outcome after temporal lobe resection

Around 20-40% of the patients show decline in verbal memory functions after TLR[72, 73] but the individual outcome is variable and difficult to predict. In fact, a small proportion of patients actually improve.[72, 74, 75] The most unfavorable outcomes have been seen after resections in the speech-dominant hemisphere.[76] Specific caution has also been expressed regarding patients with pathologies other than hippocampal sclerosis and with signs of limited cognitive reserve, who have been shown to be most at risk for continuing seizures and memory loss.[72] Studies of long-term memory outcomes after TLR from our research group have shown a stable outcome from two up to ten years postsurgically[74] while other studies show a tendency towards deterioration over time when seizure-freedom is not achieved.[72, 77]

Prediction of cognitive outcome after temporal lobe resection

As the ILAE Neuropsychology Task Force report stated, preoperative neuropsychological assessment should provide evidence-based predictions of cognitive risk associated with the proposed surgery. Two multivariate prediction models have been presented, with the purpose of predicting individual memory outcome after TLR and thereby minimizing the risk for so called "double losers", defined as patients who still have seizures postoperatively and whose memory has declined significantly.[72] These models have been able to outline the following stable risk factors for significant worsening of memory function after TLR: resection in the speech-dominant hemisphere, high preoperative verbal memory function and higher age at surgery.[78, 79] The first study by Stroup et al[78] also found that presence of other lesions than mesial temporal sclerosis and intact memory following intracarotid amobarbital injection contralateral to the seizure focus were independent predictors of verbal memory decline[78]. The second study[79] found that higher verbal intelligence quotient (IQ) was a negative predictor regarding outcomes after non-dominant TLR, while presence of cortical dysgenesis predicted significant decline in verbal learning in dominant TLR. Both models reported good specificity but the absence of cross validation of the selection procedures constitutes a limitation entailing a risk that model overfitting could have affected the performance[80].

Cognitive outcome after frontal lobe resection

Few studies have addressed cognitive outcome after FLR. Those existing show that the majority of patients do not experience substantial cognitive decline.[47, 81-86] Most studies have focused on limited aspects of cognitive function and have, for example, shown that patients with a high presurgical verbal fluency score and a resection in the language-dominant frontal lobe are most at risk of decline in verbal fluency.[84] One study found that an elevated depression score before surgery was a risk factor for decline in executive functions eight months after surgery.[83] A way to handle the heterogeneity in FLR has been to divide the subjects into subgroups by anatomical resection areas.[81, 82] These areas have been lateral, orbital, mesial and premotor/SMA (supplementary motor area) – possibly representing different functional areas as well.[81] One study found that the premotor/SMA resection group was most cognitively affected by the surgery as the patients declined in response maintenance and inhibition.[81] Language functions were negatively affected by left-sided surgery. This study was a three month follow-up and the total patient group also demonstrated decline in motor coordination and speed/attention.[81] The most comprehensive study included 90 patients who underwent FLR for epilepsy between 1989 and 2014 at a large epilepsy centre.[82] The authors concluded that the vast majority of patients who undergo FLR for epilepsy demonstrate good cognitive and motor outcome. However, a subgroup of 10% showed decline in three or more cognitive domains. They did not find any significant differences regarding demographic and epilepsy related variables including anatomical resection area between those who declined and those who did not. When declines were present, they occurred most frequently on measures of intellectual functioning (verbal and non-verbal), aspects of executive functioning (verbal fluency, perseverative behavior) visuomotor processing speed, and fine manual dexterity with the contralateral hand. The follow-up times varied from one to 15 months after surgery. None of these studies addressed extensive long-term follow-up regarding cognitive outcome after FLR.

Very few studies have investigated social cognitive abilities after FLR[87], however, the ILAE Neuropsychology Task Force report stressed that baseline levels of social cognition and 'behavioral executive functions' are specially important to address prior to FLR.[70]

Psychiatric outcomes

A meta-analysis addressing psychiatric outcomes after epilepsy surgery concluded that most patients either improved or remained stable in their psychiatric status after surgery.[88] A recent prospective longitudinal two-year follow-up after TLR found that the number of patients with a psychiatric condition decreased from 22% before surgery to 9.9% at the two-year follow-up.[89] De-novo psychiatric symptoms do occur but mostly remit within the first year after surgery.[89, 90] Seizure outcome and presurgical psychiatric history have been identified as the main predictors of psychiatric outcome.[88] Another prospective study including a control group with medically-treated epilepsy patients found that patients who underwent surgery decreased in depressive and anxiety symptoms six months after surgery, whereas anxiety levels in the nonsurgical group increased.[91] Epilepsy surgery teams need to carefully investigate preoperative psychiatric symptoms to be able to support the patients most at risk in the post-operative period and identify those who need treatment.[70, 92]

Psychosocial outcomes

Quality of life

Several studies report better health-related quality of life (HRQOL) after epilepsy surgery compared to medically treated epilepsy populations[93-97], this regards temporal as well as extratemporal surgery. Predictors of HRQOL include seizure freedom or reduced seizure frequency, mood, employment status, ability to drive and ability to stop AED.[93, 98] Most studies had follow-up periods no longer than 1-2 years while more recent qualitative data indicate that it may take at least five years for an individual to adjust psychosocially after TLR.[99] A prospective long-term follow-up study investigated HRQOL 14 years after resective epilepsy surgery.[100] The authors found that operated patients did not differ from the age- and sex-matched reference group regarding the majority of domains in the 36-item Short Form Health Survey (SF-36) but exceptions were seen in the domains of Social Functioning and Mental Health, where operated patients scored significantly lower than controls.[100] Cognitive or emotional problems were discussed as factors potentially contributing to these results.

Vocational outcome

One of the psychosocial outcomes reported is employment status, which has mostly been studied in samples of TLR patients.[101] Studies have shown that especially for those who were not employed before surgery, it takes more than two years after surgery to find employment.[102] A recent prospective and population-based long-term follow-up study found no employment gains in the whole cohort of patients after epilepsy surgery, but subgroups were found to have better outcome. Predictors for employment at any time point after surgery were identified to be preoperative employment, seizure freedom and younger age at surgery.[103]

1.4 SUBJECTIVE EXPERIENCES AFTER EPILEPSY SURGERY

So far not many studies address patients' subjective experiences of epilepsy surgery. In a study by Wilson and colleagues, patients' perceptions of surgical outcome after TLR have been found to be closely related to preoperative expectations.[104] Patients who had the most concrete expectations prior to surgery, such as being able to drive, work and participate in activities, were most satisfied, while those who expected the treatment to improve their personal independence or social relationships, were less likely to consider the surgery a success.[104] The work by Wilson et al resulted in a multidimensional model of surgical outcome where independent contributions of seizure outcome, preoperative expectations, postoperative mood and perceived success were highlighted.[104, 105] For seizure free patients, the difficulties which may be associated with discarding the sick role after epilepsy surgery were also described, a concept which in later studies has been denoted as “the burden of normality”.[106]

In a longitudinal study, 90 semi-structured interviews were held with patients and relatives with the aim to explore the trajectory of postoperative adjustment.[107] The authors investigated the incidence of symptoms related to the burden of normality over a time period of two years. Such symptoms typically appear when patients’ and relatives’ expectations on the seizure-free patient increase and new demands on social, educational, or work capacity emerge.[106] In this study, 66% of the patients reported symptoms related to the burden of normality at any time within the first two years after surgery.[107] The experiences were significantly more common in seizure-free patients than in those with continuing seizures, supporting the theory that the burden of normality is associated with the adjustment process patients undergo when trying to cope with their new “normal” life situation. Symptoms related to the burden of normality have also been shown to be more prevalent in patients with seizure onset before or during adolescence, when epilepsy has a greater impact on identity formation and the changes in self-identity are reported to be larger.[108]

Long-term studies regarding subjective experiences are rare. In a recent study, patients were interviewed 15-20 years after TLR with the aim to understand the psychosocial adjustment process at long-term.[99] The investigators found that patients experienced the first five years after surgery as stressful, trying to cope with a new situation and experiencing ‘psychological disequilibrium’.[99] After this first period, patients described how meaning-making processes led to a new sense of self-identity and normality which reestablished equilibrium. Patients also described the surgical treatment as a major turning point in life.

Patients' expectations before epilepsy surgery as well as their experiences both short- and long-term after surgery were explored in a population-based long-term qualitative study from our research group.[109] The preoperative expectations included hopes for reduction of seizures and medication, a richer social life, and improved self-confidence. However, the patients also experienced anxiety for the unknown and fear of surgical complications, as well as continued seizures. After surgery, positive experiences dominated through descriptions of increased independence, symptom reduction and relief from anxiety and worry for seizures. On the other hand, some patients described that the surgical treatment had changed their lives in a negative way due to both neurological and psychological adverse effects, regardless of seizure outcome.[109] So far there have been no studies focusing on subjective experiences after FLR.

1.5 EXECUTIVE FUNCTIONS – DEFINITION AND ASSESSMENT

Executive functions (EF) is an umbrella term including different forms of cognitive control processes, like planning and selecting from different options, ignoring non-important stimuli through persisting with the planned activity and keeping track of recently made choices.[110, 111] It also includes emotional and motivational functions.[112] The term has been debated since the definition varies and it has been argued that methodological as well as conceptual problems has made it hard to know what executive tasks measure.[112] Historically, executive dysfunction has been associated with frontal lobe injuries and the different control functions have been viewed as closely linked to functions of the prefrontal cortex (PFC).[113] However, executive functions are dependent on large networks and communication with other parts of the brain even though parts of the PFC still are considered crucial for some aspects of EF.[114, 115] Among the frontal lobe regions, the dorsolateral PFC has the strongest theoretical association to processes traditionally labeled executive by neuropsychologists (such as planning, set shifting, verbal fluency, response inhibition and working memory), while orbitofrontal regions have been found to be more important for social cognition and emotional capacity.[112] Some researchers label the different aspects of executive functions *cold* (metacognitive) versus *hot* (social cognitive, emotional) EF's.[116] In a recent study, metacognitive executive functions have been described as equated to general intelligence, which underlines the association between EF and logical thinking, abstraction and problem solving.[117]

An operational conceptualization which identified three measurable subprocesses of (metacognitive) EF was published in 2000.[118] One model relying on this conceptualization was presented in 2013 and describes three different core-EF's: inhibition and interference control, working memory and cognitive flexibility.[119]

Inhibition and interference control refer to the ability to maintain self-control by resisting temptations and staying focused on the task. It encompasses the capacity for voluntary control of attention, behavior and thoughts. These processes guide goal-oriented behavior and help us to avoid distractions as well as to take consequences into account. One traditional neuropsychological task to measure inhibitory control is the Stroop task.[120]

Working memory refers to the capacity to hold information in short term memory while manipulating and updating it.[119] To solve an arithmetic task without paper and pencil demands working memory, as well as arranging any kind of information according to a specific mental system. A task which is used to measure working memory is the Letter-number series from the Wechsler Adult Intelligence Scale – fourth edition (WAIS-IV).[121]

Cognitive flexibility refers to set-shifting capacity where different rules are to be applied at the same time and shifted between. It includes both inhibitory control and working memory and is needed to be able to shift between mental categories and different tasks in a flexible way. Neuropsychological tasks that measure cognitive flexibility are, for example, the Trail Making test (TMT)[122] and the subtest four from the Color Word Interference Test (CWIT) in the Delis-Kaplan Executive Function System (D-KEFS).[123]

From these core EF:s, higher-order EF:s are considered to be developed, such as reasoning, problem solving and planning.[124] The complexity of these processes challenges the neuropsychological tests' capacity to measure them in valid ways.[113] One way to address this difficulty has been to use complementary methods like self-rating scales or real-life observations.[125, 126]

1.6 DECISION MAKING

The case of Phineas Gage, a railroad construction worker who in 1848 had an iron rod blasted through the front of his head, forever changed our scientific and clinical knowledge regarding frontal lobe functions. Gage not only survived the explosion, he also did it with preserved intellectual capacity, memory, speech and movement.[127] What emerged after a while was however that his social behavior had changed and he started to experience social conflicts. The decisions he made were no longer advantageous for his life situation and led to social as well as economic losses. His brain lesion included the medial orbitofrontal cortex and the ventromedial prefrontal cortex bilaterally[127] and his case is considered the starting point for scientific understanding of the relation between social conduct, decision making, personality and the frontal lobes.[128, 129] Over the years, many patients with lesions in the same areas have been studied and have demonstrated about the same problems as Gage regarding social conduct and decision making. They seemed not to learn from previous experience since they made the same disadvantageous decisions over and over again, although intelligence and other cognitive functions were preserved in neuropsychological testing.[130] The first task to succeed in measuring these difficulties was the Iowa Gambling Task (IGT), developed in 1994 by Antoine Bechara and coworkers.[131] It is thought to mimic real-life decisions and thereby reveal difficulties which previous tests had not been able to uncover. It is now one of the most widely used tasks to measure decision-making impairments in many different populations and a good example of how development of new tasks is necessary to increase our scientific knowledge in areas where existing methods are insufficient.

The concept of decision making is divided into *decision making under ambiguity* and *decision making under risk.*[132] Decision making under ambiguity refers to a situation where rules are implicit and the individual needs to rely on emotional feedback processes to reach the best decision. This kind of decision making is often measured with the IGT.[133] Decision making under risk relies on primarily cognitive processes and refers to a situation where the options are explicit and the outcomes are either estimated or clearly provided.[134]

Decision making in epilepsy

Decision-making capacity has not been extensively studied in epilepsy populations. Existing studies on PWE primarily focus on decision making in TLE and show that these patients have difficulties with decision making under ambiguity while they can manage decision making under risk.[135-137] TLE patients demonstrated a failure to learn throughout the IGT and the authors argue that the high percentage of implicit memory deficits in this population could contribute to these difficulties.[135] Another potential mechanism is that the emotional processes embedded in the more implicit decision making under ambiguity are related to pathogenic mechanisms in the limbic system in TLE.[135, 136] No consistent correlations have been found between decision-making capacity and epilepsy related variables such as seizure frequency, lateralization or age at epilepsy onset, nor between decision making and cognitive functions.[136] Two studies addressed decision making after epilepsy surgery.[138, 139] The conclusions in these studies suggest that patients having gone through a TLR might be more severely impaired in decision-making capacity than non-operated TLE patients.[136] However, these studies only included postoperative data. Studies of decision making in juvenile myoclonic epilepsy and other generalized epilepsies are rare and show diverging results.[140, 141] Decision making in FLE or after FLR has so far not been studied at all.

2 AIMS

The overall aim of this thesis was to further the knowledge about the neuropsychological consequences of resective epilepsy surgery. Even though worsening of verbal memory after TLR is the most well-known expected adverse cognitive effect, it is difficult to make individual predictions about the degree of impairment. For FLR, knowledge about the cognitive consequences is still scarce and needs to be further explored to improve preoperative counselling. The aims of this thesis were therefore to develop an individualized prediction model for verbal memory decline after TLR and to improve knowledge about cognitive, emotional and psychosocial functions after FLR.

The specific aims were:

I. To develop a prediction model for verbal memory decline after TLR for epilepsy.

II. To investigate the cognitive outcome two years after FLR for epilepsy.

III. To explore both patients' and relatives' experiences of cognitive, emotional, and psychosocial functions after FLR.

IV. To explore decision making after FLR for epilepsy.

3 PATIENTS AND METHODS

3.1 STUDY DESIGN

All studies were observational cohort studies.

In study I, a prediction model was developed based on cognitive data from a prospective cohort of tested patients. Study II was a prospective cohort study, while studies III and IV were retrospective cohort studies.

The thesis included three studies based on quantitative cognitive measurements (Studies I, II and IV) and one study based on qualitative data derived from individual interviews (Study III).

3.2 SUBJECT SELECTION

Participants in the studies were consecutive patients enrolled in the epilepsy surgery program at Sahlgrenska University Hospital in Gothenburg, Sweden. They had all completed a comprehensive neuropsychological assessment before and two years after TLR or FLR. Two different control groups were used, consisting of 25 (study I, II) and 30 (study IV) healthy persons respectively. For the qualitative study (Study III), relatives to the patients were also interviewed.

Study I

One hundred and ten patients from a consecutive series of 123 patients who had undergone TLR for epilepsy between 1987 and 2011 were included in the study. Exclusion criteria were missing data in the outcome variable (11 patients) and atypical language representation identified in two patients through the Wada test (selective injection of a barbiturate in the internal carotid artery to induce a temporary state of hemianesthesia, during which language functions of the unaffected hemisphere are tested).[142, 143] They were all neuropsychologically assessed preoperatively and two years after surgery, with a mean test interval of 2.7 years. Forty-five % of the patients had a left-sided TLR and 61% were seizure-free during the last year (with or without aura, ILAE class 1 and 2[144]) at the two-year follow-up.

To determine reliable change indices (RCI), data from a previously collected control group of 25 neurologically healthy persons was used.[32] The groups did not differ statistically regarding age at baseline, whereas the test interval was longer in the control group (M = 3.1, SD = 0.2, compared to M = 2.7, SD = 0.8, *p*-value = 0.000). Controls were recruited among the patients' friends, colleagues and spouses, i.e., persons with similar age, socio-cultural circumstances and length of education.

Study II

A consecutive cohort of 30 patients who had undergone FLR for epilepsy between 1989 and 2011 were included in the study. They had completed a comprehensive neuropsychological assessment preoperatively and two years after surgery (mean test interval 2.5 years). Thirteen patients had surgery in the speech-dominant hemisphere. At the two-year follow-up, 15 patients (50%) were seizure-free. The patient group was further divided into four anatomical subgroups; premotor/SMA, lateral, mesial and orbital. The mesial and orbital groups were merged into one due to small sample sizes. Two patients had large resections and were therefore excluded from subgroup analyses.

The control group was the same as in study I and did not differ from the FLR patients regarding age, education or test interval.

Study III

Fourteen patients from a consecutive sample of 20 patients who had undergone FLR between 2000 and 2016 were included in the study. Nine of these patients were also included in study II, se Figure 1. The sample size was set to reach a sufficient level of *information power* considering factors like study aim, sample specificity and theoretical background[145] when deciding upon sample sizes in qualitative research. Time from resection to interview varied between two and 15 years (median = 11 years). The dropouts consisted of three patients who declined participation and three who were unreachable. Seventy-one percent of the patients were seizure-free at the time of data collection.

Twelve close relatives (six parents, five partners, one aunt) of the patients were included. One patient did not have any relatives who could participate, and for the single relative of another patient practical issues precluded participation. The relatives were selected in dialogue with the patients and the inclusion criterion was that they should have known the patients well before and after the surgery.

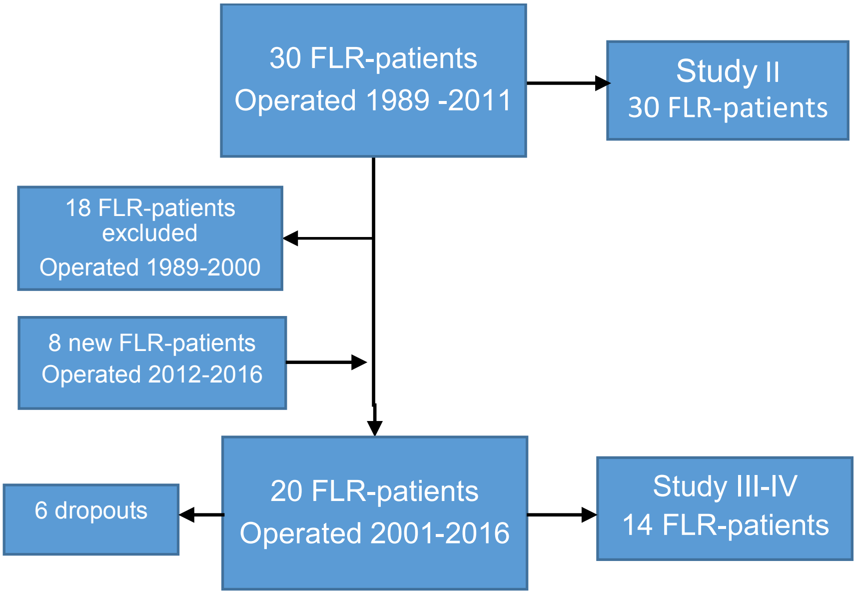

Figure 1. Flow chart over FLR patients included, excluded and dropouts in Study II-IV.

Study IV

The patient group consisted of the same 14 FLR patients as in study III.

The control group consisted of 30 healthy persons who did not differ from the patient group regarding age, gender or level of education. Data from the control group was collected in 2018 and 2019.

3.3 NEUROPSYCHOLOGICAL ASSESSMENTS

Psychometrical properties in included measures

Throughout this thesis, we have included neuropsychological tests with good psychometrical properties. Special attention has been given to test-retest reliability for studies including repeated measures where test-retest coefficients are between 0.79 and 0.95 according to test manuals referred to in the following sections. Tests in studies I and II have been included according to standard neuropsychological batteries developed for epilepsy surgery assessment at the starting point of data collection. Compared to modern recommendations[146] they are still considered adequate.

General intellectual functions

In study I and II the Wechsler Adult Intelligence Scale – revised (WAIS-R) was used to measure level of intellectual function.[147] In study IV different versions of the WAIS (WAIS-R, WAIS III) were used as background data regarding level of intellectual function.[147, 148] WAIS-R includes three different IQ measures; Full scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ). WAIS III provides, in addition to FSIQ, VIQ and PIQ, four indices; Verbal Comprehension Index (VCI), Perceptual Organization Index (POI), Working Memory Index (WMI) and Processing Speed Index (PSI). Only FSIQ was used in study IV.

Verbal memory

Two different verbal memory tests were used. In *Claeson-Dahl Learning and Retention Test (CD)* a word list of 10 words is read aloud to the patient who is instructed to remember as many words as possible and recall them after a 15-second delay. The words are repeated until the subject either has recalled the whole list twice successively or has had 10 trials. The weighted sum (WS) reflects the total learning capacity. After a delay of 30 minutes, the patient is once again asked to recall as many words from the word list as possible, which reflects the delayed recall (DR), measured in percent of the maximum learning capacity [149]. The *Cronholm-Molander (CM)* word paired associates assesses recall for 30 associated word-pairs. Retention is assessed immediately (immediate recall, IR), and after three hours (DR).[150, 151] The test consists of three series, with 10 paired associated words each. After presenting 10 pairs, the test leader gives the first word of the pair and the subject is asked to recall the second word from memory. After three hours, the same procedure is repeated to assess DR. In both tests, alternate versions were used to avoid practice effects. In study I, both verbal memory tests were included in the initial regression analysis while the prediction model was based only on the CM paired associates IR. In study II, only the CM paired associates DR was used.

Visual memory

The *Rey-Osterreith Complex Figure test (ROCF)* was used in study II [152]. In this task, the subject is instructed to copy a complex visuospatial figure by drawing it, then draw it from memory after a five minutes distraction and again after 30 minutes delay (DR). The results from the 30 minutes delay were included in the study.

Speed and attention

In study II, the *Trail Making Test (TMT) A and B* from the Halstead-Reitan Battery was used.[122] Part A measures psychomotor speed when the subject connects numbers as fast as possible in sequencing order while part B also measures aspects of mental flexibility as numbers and letters are sequenced every other time (1-A-2-B etc.). In study II, two subtests from WAIS-R measuring auditive attention and processing speed were used.[147] *Digit Span* forward requires that the subject repeats numbers in a certain order, which demands verbal attention capacity. *Digit Symbol* requires the subject to transcribe the symbols paired with the numbers 1-9 as quickly as possible, within a time limit. The test demands processing speed as well as sustained attention and visuomotor coordination.

Verbal functions

Two subtests from WAIS-R measuring different aspects of verbal cognition were used in study II.[147] *Comprehension* measures semantic knowledge and verbal reasoning ability where the subject is asked to explain different phenomena in society. *Similarities* measures verbal concept formation since the subject needs to find an abstract similarity between two words. Two different versions of verbal fluency tasks were used in study II: *Controlled Oral Word Association Task (COWAT)* and the *Chicago Word Fluency Test (CWFT)*.[110, 152] These tests measure an individual's capacity to produce as many words as possible beginning with a given letter within a time limit. For COWAT the production is oral and for CWFT it is written.

Executive functions

In study II the subtests *Digit span* backwards and *Arithmetic* from WAIS-R were used.[147] They both require working memory capacity as information is to be held in short-term memory while operated on. In *Digit span* backwards, numbers are read aloud to the subject who should remember them and answer by repeating them in reversed order. In *Arithmetic* the subject is asked to solve arithmetic word problems without pencil and paper which demands working memory as well as arithmetic skills and attention capacity. It also demands processing speed since the tasks have time limits. The subtest *Picture Arrangement* from WAIS-R was also used in study II.[147] The subject needs to look at several (three to six) cards and arrange these in order according to what happens on the cards (together they tell a little story). The test has been thought to rely on anticipation and planning capacity as well as social judgment skills.[153, 154] Study II also included TMT B, which is described above and requires processing speed, visual attention and executive attention since letters and numbers on a paper sheet should be connected every second time.[122]

The *Color Word Interference Test (CWIT)* subtest 3 and 4 and the *Sorting Test* from the D-KEFS were used in study IV.[123] The CWIT is a developed version of the classical Stroop Task.[120] In subtest 3 color-words are written in a conflicting color (i e the word blue is written in red ink) and the subject should name the color of the ink. This demands inhibitory control and processing speed; the result is measured in seconds to completion. In subtest 4, both inhibitory control and cognitive flexibility is tested since subjects need to switch between naming ink color and reading the words. The Sorting Test demands concept formation skills and divergent thinking as six cards should be sorted into two different categories with three cards each, in as many ways possible. A working memory task was also used in study IV: The *Letter-number-series* from WAIS IV[121] where the test leader reads a series of mixed numbers and letters aloud to the subject and the subject should answer verbally through ordering the series with the numbers first in numerical order and then the letters in alphabetical order.

Visuospatial and perceptual functions

Two subtests from the WAIS-R which require visuospatial construction and analysis skills were used in study II.[147] *Block design* demands visuospatial perception and construction skills since the subject has to copy two-dimensional patterns with cubes. *Figure Assembly* is a puzzle task where subjects are to conjoin separate parts to build a motive.

Decision making

To measure decision-making capacity, subjects completed the computerized version of the *Iowa Gambling Task (IGT)*.[131] In this task, subjects are instructed to pick cards from four decks over a total of 100 trials with the goal of winning as much fictitious money as possible. They are instructed to treat the pretend money as real money so the decisions made should resemble real life decisions as much as possible. Two of the four decks (A and B) are associated with high immediate rewards but large losses and are disadvantageous in the long run. The other two decks (C and D) are advantageous since they provide smaller immediate rewards but even smaller losses and thereby offer a better long-term outcome. Participants are unaware of which decks are advantageous but they are told that some decks are worse than others. Success on the IGT depends on the ability to learn from feedback during the task by implicit understanding of the disadvantageous effects of decks A and B.

The results on the IGT are described in the Total Net Score which is calculated by subtracting the number of cards selected in the bad decks

(A and B) from the number of cards selected in the good decks (C and D). This score describes the total performance on the task. Net scores above zero indicate advantageous and below zero disadvantageous decision making. Furthermore, the total trials of the task are divided into five consecutive blocks (net 1-5) with 20 trials each and apart from looking at the Total Net Score, each of the five blocks can be analyzed separately to investigate the learning profile across the task. Healthy subjects typically get better at avoiding the disadvantageous decks over time and therefore end up with a positive Total Net Score, while patients with diseases or injuries affecting the frontal lobe can show the opposite pattern[131]. In study IV, the Total Net Score, net scores from the five different blocks, and a change value which is calculated by subtracting the score in block 1 from the score in block 5 were used. A higher net score in block 5 than in block 1 suggests improvement in decision-making performance. Therefore, a positive change score shows improved performance across the blocks, while a negative change score indicates a failure to learn.

Self-rating scales

In study IV, three self-rating scales were used: the *Mental Fatigue Scale (MFS)*[155], the *Hospital Anxiety and Depression Scale (HADS)*[156], and the *Frontal Systems Behavior Scale (FrSBe).*[157] The scales were included since fatigue, depression and frontal lobe dysfunction have been reported to affect decision making.[158, 159] These are also symptoms shown to be present in FLR patients.[83] The HADS is a 14-item scale where seven items are related to anxiety symptoms and seven to depressive symptoms. Cut-offs regarding pathological degree of symptoms are presented for each subscale. The HADS has shown good psychometric properties on construct validity for epilepsy populations.[160, 161] The MFS is a 14-item scale measuring symptoms of mental fatigue such as difficulties getting things done, low stress tolerance and mental exhaustion, clinical cut-offs for different degrees of fatigue severity are presented.[155] The FrSBe was used to explore behavior typical of frontal lobe damage/dysfunction.[125, 162] The FrSBe consists of three different subscales representing apathy, dysexecutive behavior and disinhibited behavior. For each subscale, as well as for the total scale, a cut-off is set to represent clinical level of symptoms.

3.4 QUALITATIVE METHOD

In study III, patients and relatives were interviewed with a semi structured approach with questions covering aspects of perceived changes in emotion, cognition and psychosocial abilities after FLR. Interview guides were developed based on the aim of the study and clinical experience. They are presented in Supplemental material in Paper III. Examples of questions asked were ‘‘Since surgery, have you experienced any changes regarding your emotional abilities?” and “Is there anything in your relatives’ ‘‘former me”, that is before surgery, that you miss?”. Interviews were audio-recorded, transcribed and analyzed with qualitative content analysis (QCA) which was chosen since the study was explorative in nature[163, 164] and QCA is a suitable structured method to study areas which are previously unknown. Data analysis was inductive, meaning that no theoretical framework was used but the subjects’ own words were leading the analysis.[165] After reading the text several times, it was divided into meaning units and then into codes. The codes were sorted into sub-categories and for further abstraction into categories representing the manifest (literally present) content. Finally, the categories were further abstracted and interpreted into a theme representing the latent content, the underlying meaning of the text.[164, 166] To reassure trustworthiness during the analysis process, parts of the data were analyzed by two of the authors independently and then all authors jointly reflected on and discussed the meaning of the codes, the naming of the categories and the resulting theme. The authors also had different pre-understandings of the subject which reduced the risk for theoretical bias in the analysis.[163] The process of data analyses in QCA is visualized below.

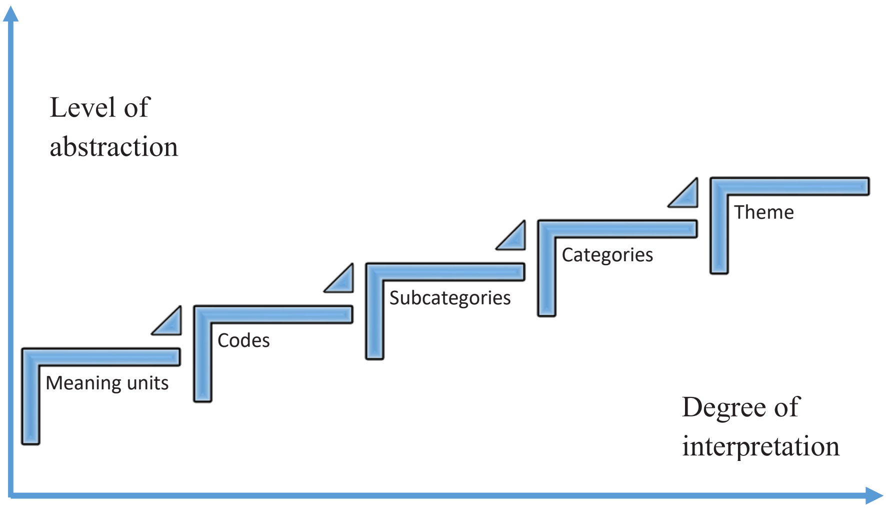

Figure 2. Process of data analysis in QCA

3.5 STATISTICAL ANALYSES

Raw scores were analyzed (except for the sum scores of FSIQ, VIQ and PIQ). To describe distribution, median and interquartile ranges (studies II and IV) and mean and SD (studies I and II) were used. Missing data were not replaced by group or subgroup means. To obtain change scores, baseline scores were subtracted from follow-up scores (studies I and II). Due to small sample sizes in the studies II and IV, non-parametric methods were used.

In study I, RCI indices were used to define reliable negative change in verbal memory performance. Confidence intervals of 90% based on the RCI values were used. Penalized logistic regression methods were chosen in the development of a clinical prediction model of memory decline. This was considered superior to logistic regression because of the small number of events (n=22) in relation to the number of candidate predictors. It is also recommended in the TRIPOD checklist for development and validation of prediction models.[167] In general, penalized methods are considered to handle the risk for overfitting better. A penalized method called lasso[167, 168] was used, performing both model selection and shrinkage.

The stepwise selection procedure in study I was evaluated using 20 x 10-fold cross-validation. Statistical analyses were performed using JMP3.3.00, IBM SPSS statistics 23 and R v. 3.5.2. Cross-validation was implemented in R, using the glmnet package v. 2.0-16 for estimation of logistic regression models using lasso.

In study II, data analysis was nonparametric due to the small sample size. As descriptive statistics means, SD, medians, and interquartile ranges were used. The Kruskal–Wallis Test for multiple samples was used in between-group comparisons of change scores and the Mann–Whitney U-test for subsequent two samples comparisons. For variables with a significant difference in the change scores, the effect of baseline scores on the relationship between presence of epilepsy and change in performance was controlled by using binary logistic regression. The dependent variable was presence of epilepsy and the coefficient for the cognitive variable was adjusted by forcing the scores from the baseline performance into the regression model. These group comparisons were made both for the total FLR group and for the three subgroups (lateral, premotor/SMA and orbital/mesial). At the individual level, analyses were made using RCI. The RCI analyses were based on the test-retest data (baseline to two-year follow-up) of the control group using the method of Jacobson and Truax.[169] In addition, Bayesian point estimate was used to describe the level of abnormality of individual scores in relation to the control group. The computer program BTD_Cov_Raw.exe and SPSS version 22 were used.

In study IV, non-parametric methods were used due to the small sample size. The Mann-Whitney U-test and the Fishers' exact test were used for between-group comparisons. For correlation analysis, Spearmans' rho was used. Correlation coefficients between .30 and .49 were considered as moderate and correlations ≥ .50 as strong.[170] The individual results were compared to published norms. Clinically meaningful impairment was defined as a level of 1.5 standard deviation or more from the mean. For self-rating questionnaires, cut-off values described in manuals or other generic material were used to establish clinical impairment. Statistical analyses were performed using IBM SPSS Statistics 23.

3.6 ETHICAL CONSIDERATIONS

All studies included in this thesis have been approved by the regional Ethics board in Gothenburg.

Special attention has been given to guarantee the anonymity of the participants in the qualitative study, since they constitute a small patient sample and the data presented are more personal than in quantitative studies.

4 RESULTS

4.1 SUMMARY OF STUDY I

Predicting verbal memory decline following temporal lobe resection for epilepsy

Using RCI values, 20% of the TLR patients (n=22) were identified as having declined significantly pre- to postoperatively in the verbal memory task used. Fourteen of these patients had a left TLR (change score M = -11.86, SD = 0.937) and eight a right TLR (change score M = -8.63, SD = 0.653). Multivariable logistic regression models with a decline in verbal memory as the dependent variable are described in Table 1. Selected variables, parameter estimates and AUC obtained by stepwise selection and the different versions of lasso are presented in the Table. The estimation procedures are reasonably concordant and identified three strong predictors for verbal memory decline. These were side of surgery, inclusion of hippocampus in the resection and preoperative verbal memory score.

Table 1. Prediction models selected by stepwise selection, lasso, adaptive lasso and tresholded lasso.

	Logistic regression coefficients			
	Stepwise selection	Lasso	Adaptive lasso[a]	Thresholded lasso[b]
Intercept	−9.09	−6.29	−6.78	−8.95
TCS (yes)		0.35		
Inclusion of hippocampus (yes)	2.83	2.06	2.03	2.78
Side of surgery (LTL)	1.89	1.20	1.15	1.85
CDWS		−0.0025		
CDDR		−0.0047		
CMIR	0.22	0.16	0.16	0.22
ROC AUC	0.83	0.85	0.83	0.83
20 × 10-fold CV, mean ROC AUC	0.69	0.72	0.71	0.74

Abbreviations: AUC, area under the curve; CDDR, Claeson-Dahl delayed recall; CDWS, Claeson-Dahl weighted sum; CMIR, Cronholm-Molander word paired associatesimmediate recall; CV, cross-validation; LTL, left temporal lobe; ROC, receiver operating curve; TCS, focal to bilateral tonic-clonic seizures.

[a]Regressioncoefficients estimated with ordinary multivariable logistic regression were used as initial estimates in the adaptive lassoprocedure.

[b]Parameters with initial lassoestimates greater than 0.60 per standard deviation (SD)were included in the model. The cut-off at 0.60 per SD yielded the optimal model in terms of Akaike's information criterion (AIC).

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Cross-validation identified the tresholded lasso with three variables as the best model with a mean cross-validation AUC at 0.74, the lasso with six variables was identified as second best (mean cross-validation AUC 0.72), Table 1 (see also Paper I, Figure 1).

Further testing of the three-variable model and the six-variable model was performed to examine if inclusion of more variables could add clinical value. When both models were re-estimated by lasso, the coefficient for one of the preoperative memory variables: the CDWS shrunk to zero. Since the explaining value of the other memory variable from the same test was only 3%, both these memory variables were excluded from further analysis. This resulted in two models to test: a) a three-variable model and b) a four-variable model. The final lasso estimates on these models are shown in Table 2.

Table 2. Prediction of the two best regression models based on the complete cohort (n = 110).

Term	Estimate	Standardized estimate[a]	*P*-value
Four-predictor model			
Intercept	−8.6	−2.03	<.0001
Preoperative memory	0.2	12.12	.0002
Inclusion of hippocampus	2.54	13.19	.0007
Side of surgery	1.93	10.07	.0018
Presence of TCS	1.02	5.25	.0537
Three-predictor model			
Intercept	−7.72	−1.94	<.0001
Preoperative memory	0.19	11.73	.0002
Inclusion of hippocampus	2.14	11.11	.0046
Side of surgery	1.9	9.91	.0014

Abbreviation: TCS,focal to bilateral tonic-clonic seizures.
[a]Centred and scaled predictors.

Ljunggren et al. (with permission) Acta Neurol Scand 2019; 140:312-319.

The four-variable model was found to be of superior clinical value since it discriminated better between the response-groups as presented in Figure 3. The final model stated that left-sided surgery, inclusion of hippocampus in the resection, a high preoperative verbal memory score and a history of tonic-clonic seizures (TCS) were associated to post-operative decline in verbal memory. The model sensitivity was 82% and the overall accuracy was 70-85% depending on the risk threshold chosen.

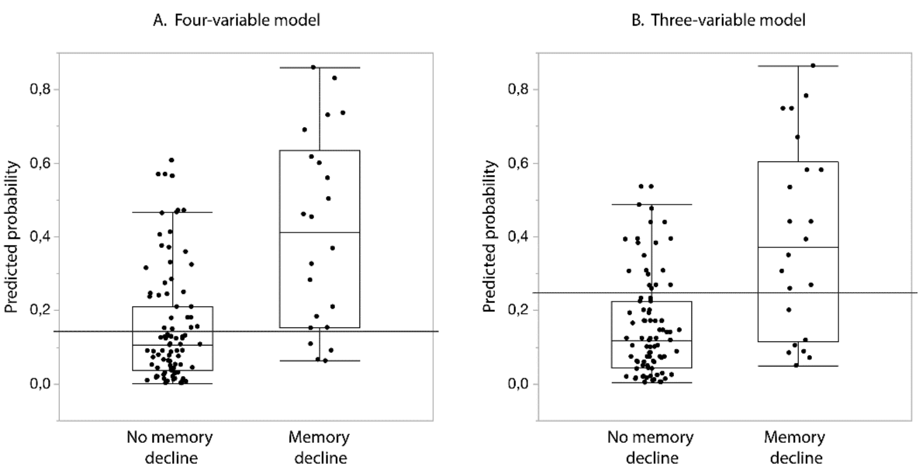

Figure 3. The distribution and corresponding box-plots for observed versus predicted values for (A) the four-variable model and (B) the three-variable model. The horizontal line represents the "optimal" risk threshold level based on the following formula: sensitivity-(1-specificity). AUC values: A, 0.82, B, 0.79. Ljunggren et al. (with permission) Acta Neurol Scand 2019; 140:312-319.

4.2 SUMMARY OF STUDY II

Cognitive outcome two years after frontal lobe resection for epilepsy – A prospective longitudinal study

Before surgery, the patients performed worse than controls on tests measuring speed, executive functions, global and verbal intelligence. No differences were present at baseline between the subgroups with different localization of the resection (*p*-values between .216 and .971).

At the two-year follow-up only one variable showed a significant difference regarding the change values between the patient and control group; in Figure Assembly the median change for the patient group was -1.5 while the control group median was 2.0 (*p*-value .028). At subgroup level, significant differences between the change scores were present for FSIQ and the subtest Comprehension. The lateral resection group had less improvement in FSIQ than both controls (*z*-value -2.061, $p = .037$) and the mesial/orbital subgroup (*z*-value -2.449; $p = .014$). The premotor/SMA subgroup had less improvement in FSIQ than the mesial/orbital subgroup (*z*-value -2.2, $p = .035$).

At the individual level, a combination of RCI indices and Bayesian point estimates were used to investigate possible clinically meaningful decline. For the vast majority of neuropsychological variables used in this study the results did not show clinically relevant change as 74-100% of the individual scores were classified as non-reliable change and/or within the normal range. One exception concerned the subtest Comprehension from WAIS-R where 8/18 (44%) of the patients showed a reliable decline. These patients belonged to either the lateral (4/7 patients) or the premotor/SMA (4/7 patients) subgroups as illustrated in Figure 4.

The main result of the study was cognitive stability two years after FLR for epilepsy. The lateral resection group had less improvement than controls in FSIQ and at the individual level 44% (8/18) of the patients had a reliable decline in verbal reasoning ability. This decline was present in the lateral and in the premotor/SMA resection groups and was not affected by side of surgery or seizure outcome.

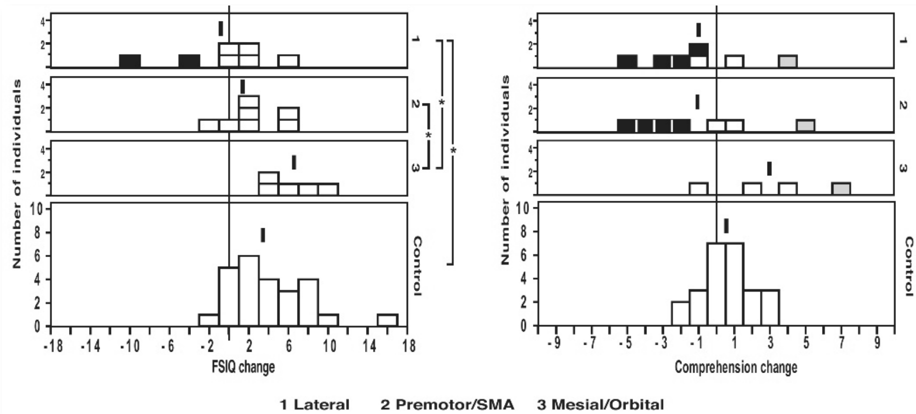

*Figure 4. The distribution of the control group and of the individual scores from the three resection groups (lateral, premotor/SMA, and mesial/orbital). FSIQ = Full Scale IQ; ■ = reliable decline and estimated percentage in the control population <7%; ■ = reliable improvement and estimated percentage in the control population 93%; ▌=group mean value; * = p < .05. Ljunggren et al. (with permission) Seizure 30 (2015) 50–56.*

4.3 SUMMARY OF STUDY III

Experiences of emotional and psychosocial functioning after frontal lobe resection for epilepsy

Three categories emerged regarding experiences of emotional and psychosocial functioning after FLR for epilepsy, based on the qualitative content analysis from interviews with patients and relatives. These were *Increased zest for life, Withdrawal from social interaction* and *Deal with a changed everyday life.* These categories were further abstracted into the main theme *Finding contentment in success and setbacks* which reflected both the positive and negative experiences described by patients and relatives after the neurosurgical treatment. Table 3 presents the main theme, three categories and six sub-categories.

Table 3. Conceptual map of the data including main theme, categories and subcategories.

Theme	**Finding contentment in success and setbacks**		
Categories	Increased zest for life	Withdrawal from social interaction	Deal with a changed everyday life
Subcategories	Emotional access and feelings of relief A risk worth taking	Loss of energy and lowered mood Reduced ability to experience and express emotion	Plan for shortcomings Thoughts about causality

Ljunggren et al. adapted from Epilepsy & Behavior 121 (2021) 108077

Among the most positive experiences, primarily in seizure-free patients, were feelings of increased autonomy and a sense of a new grown-up identity, as well as gratitude and relief that the surgical treatment had turned out so well. A new maturity was experienced alongside increased self-awareness and empathy. Patients also described that it was easier to feel and express emotions and that they could enjoy life more. They described a more optimistic attitude after the operation. Not having to fear the occurrence of seizures was important and led to a more relaxed attitude and increased social skills. Relatives highlighted the new-won autonomy among the patients and that they seemed to be happier.

At the negative end of the spectrum, both the patients and their relatives brought up descriptions of energy loss, social withdrawal and lowered mood among the patients. This was irrespective of seizure freedom and partly experienced as a negative side-effect of the surgical treatment. Some patients accepted their reduced energy and arranged life according to the new prerequisites, while others (both patients and relatives) had more difficulties coping with the changed circumstances. Relatives described that they missed their previously happy and spontaneous family member and expressed sadness over the reduced ability to take part in social life. Some patients also described a reduced capacity to feel passionate which led to more withdrawal since they did not get the emotional feedback from doing things they used to like.

The patients generally considered the surgical treatment to be a risk worth taking and also commented on the fact that other variables such as increasing age and side-effects from ongoing medical treatment also might have reduced energy just as much as the surgical treatment.

4.4 SUMMARY OF STUDY IV

Decision making after frontal lobe resection for epilepsy

The FLR group demonstrated a lower median for the Total Net Score in the IGT compared to the controls (FLR group median = 4; control group median = 40), although this was not significant (p = .055). When analyzing the separate parts of the IGT performance, there was a significant difference between the groups regarding the last block where the FLR group had a negative median value (FLR group median = -6) while the control group median was 14 (p = .001). There was also a significant difference regarding the change value which reflected learning throughout the task (FLR group change median = -5; control group change median = 14, p = .005). These results reflected that the FLR patients showed a failure to learn throughout the task and had not improved in decision making at the end of the task, which the controls had. This is demonstrated by Figure 1 in paper IV which shows that the controls improve from block 1 to block 5 while FLR patients show a trajectory in the opposite direction.

To investigate associations between decision making and executive functions, correlation analyses were made. Moderate correlations were observed between the IGT change score and performance on CWIT 3 (rho = -.433), the Letter-number-series test (rho = .313) and HADS depression (rho = .412), although none of the correlations reached significance.

The patients performed worse than the controls in three out of four executive tasks (cf Table 3 in Paper 4), this concerned the subtest 4 from CWIT measuring inhibitory control and cognitive flexibility, the Letter-number-series from WAIS IV measuring working memory and the Sorting Task from D-KEFS measuring concept formation (p-values between .000 and .011). However, only a minority of patients' scores were considered clinically impaired when compared to standardized norms.

Regarding self-rating scales, the patients' scores differed significantly from the controls' in FrSBe subscales for apathy and disinhibition as well as for the total FrSBe score (p-values between .000 and .015, cf Table 3). Even here, few patients demonstrated scores that represented a clinically meaningful level of symptoms when compared to cut-off scores presented in manuals and other generic material.

5 DISCUSSION

The aims of this thesis were to develop an individualized prediction model for verbal memory decline after TLR and to improve knowledge about cognitive, emotional and psychosocial functions after FLR. Our prediction model identified side of surgery, inclusion or not of hippocampus in the surgery, preoperative verbal memory score and a history of TCS as predictors for verbal memory decline after TLR. We could demonstrate that cognitive function is, at group level, primarily stable two years after FLR. Through the interview study we could present patients' and relatives' positive as well as negative experiences of emotional and psychosocial functions after FLR. Finally, we could show that patients had difficulties with decision making after FLR and that they demonstrated a failure to learn throughout the IGT, which may have implications for life after surgery and rehabilitation after FLR.

5.1 PREDICTION OF COGNITIVE OUTCOME AFTER TLR

Prediction models of cognitive decline in epilepsy surgery are still rare and all but one concerns memory decline after TLR.[78, 79, 171, 172] This is not surprising since neuropsychological research in the field of epilepsy surgery has been dominated by studies regarding memory deficits after TLR.[74, 76, 77] TLR is also still the most common epilepsy surgery procedure. Memory problems are important to assess and to predict since they have an impact on work capacity as well as private life. Our prediction model was concordant with findings from previous models regarding side of surgery, the presence of hippocampus in the resection and preoperative verbal memory score as predictors for postoperative decline in verbal memory.[78, 79] However, we could not replicate findings that older age at surgery, other lesions than mesial temporal sclerosis or higher VIQ represented higher risk for verbal memory decline. Our model also identified a predictor not identified in previous studies, which was the presence of TCS before surgery. We interpreted this as a sign of more wide-spread epileptic activity, potentially covering larger networks in the brain and therefore rendering individuals more vulnerable to cognitive decline.

Our model is the first to be used in the Swedish context and it will be valuable when counselling the individual patient and his/her family before a potential TLR. It will make it possible to better predict an individual's risk of memory impairment and how this would affect the person in daily life. This would help both the epilepsy surgery team in the counselling process and the patient to make an informed decision about surgery.[70]

5.2 COGNITIVE OUTCOME AFTER FLR

In study II we found mainly cognitive stability two years after FLR. This is an encouraging result since it indicates that the surgical treatment does not cause major cognitive decline at group level. This is concordant with previous findings.[81, 82] It also adds a perspective regarding cognitive stability over time after FLR since this study has the longest follow-up so far regarding cognitive outcome after FLR. The ILAE Neuropsychology Task Force report on the role of neuropsychology in epilepsy surgery stated that the longer the follow-up, the more accurate the picture of the postoperative outcome.[70]

One previous three months follow-up study divided the heterogeneous FLR group into anatomic subgroups, possibly also representing different functional areas.[81] The study found that patients with resections in the premotor/SMA region and patients with precentral/central multiple subpial transections (MST) had additional impairment after surgery.[81] The premotor/SMA resections resulted in a larger decline in response maintenance and inhibition and left-sided resections also led to deterioration in language functions. The latter observation was clearly related to transient aphasia directly after surgery. Precentral/central MST led to more problems with motor coordination and this group also had worse seizure outcome than the other groups. Over all, seizure freedom was related to significantly improved short-term memory functions among FLR patients, interpreted as a release of function from frontal areas not affected by surgery.[81]

In our two-year follow-up study, we used the same anatomical subgroups as in the above-mentioned study, but could not replicate their findings. One possible explanation for this could be the different follow-up times in the studies, three months versus two years. Three months after epilepsy surgery, acute effects such as fatigue or psychiatric symptoms are more likely to be present and may have affected the cognitive results.[90] The neuropsychological methods used were also partly different.

Our findings at subgroup level indicated that resections in lateral or premotor/SMA areas resulted in a significant decline in verbal reasoning, irrespective of which hemisphere that had been operated. We could also show that patients with resections in lateral frontal areas had less improvement in FSIQ in the WAIS-R, compared to controls and other FLR subgroups. We interpreted this to possibly result from a lack of practice effect. To investigate whether declines were common at an individual level we calculated clinically meaningful change for each variable and each individual. The finding from this analysis showed that a large proportion (44 %) of the individuals had a decline in the subtest *Comprehension* measuring verbal reasoning ability. This finding was unexpected. These individuals had more difficulties answering some of the questions postoperatively and some of their answers were not as elaborate or complex as they had been preoperatively. This could be understood as a difficulty elaborating thoughts or ideas into verbal answers. Language deterioration could have an impact on a result like this, but we found no differences regarding side of resection. The

Comprehension subtest from WAIS-R has traditionally been regarded to be related to “social intelligence” since it measures well-learned social conventions[173], however, the accuracy of these assumptions has been questioned.[174]

The largest study so far regarding cognitive outcome after FLR was published in 2017 by Busch et al[82] and included 90 patients. Results were analyzed both at group and subgroup level and showed that 48% of the patients demonstrated no reliable postoperative decline in cognition, according to RCIs developed from repeated testing of epilepsy patients. Forty-two % demonstrated decline in one or two cognitive domains, while the remaining 10% demonstrated reliable postoperative decline in three or more cognitive domains. Declines were most often seen in intelligence measures, executive functions (verbal fluency, perseverative errors), visuomotor processing speed, or fine manual dexterity with the contralateral hand. No relation was found between anatomical site or size of the resection and cognitive outcome apart from SMA resections which gave rise to reduced fine manual dexterity in the hand contralateral to resection.[82] The finding of a subgroup of 10% with reliable postoperative decline differs from previous studies, including ours, where cognitive stability was the main result. The larger patient sample might be one explanation for this finding, as well as the larger resection sizes. The authors describe that around 80% of the patients had undergone large resections which included two or more frontal lobe regions.[82] They also used RCI-values specific for epilepsy which might result in different conclusions since the test-retest reliability has been found to differ from healthy controls regarding some cognitive measures.[175]

In conclusion, few findings support that resections in different anatomical subregions of the frontal lobe should result in different cognitive outcomes. This is concordant with more recent network theories which underline the complexity of the frontal lobes and executive functions.[176] More research is needed since existing studies are mainly based on small patient samples, with restricted follow-up periods.[81, 83, 84] Furthermore, use of different cognitive measures in the studies increases the uncertainty of the results and makes it hard to draw solid conclusions. The neuropsychological batteries in epilepsy surgery centres (including ours) have been developed mostly from a TLR perspective and typically include few methods for assessment of frontal lobe functions. New protocols are warranted which cover more aspects of cognition to improve assessment of patients with FLE.

5.3 SUBJECTIVE EXPERIENCES AFTER FLR

Due to the lack of studies addressing subjective experiences after FLR, an interview study was made with the aim to explore patients' and relatives' experiences of cognitive, emotional and psychosocial functions after FLR. This was considered a valuable complement to the standardized neuropsychological assessment which had not been able to identify reported problems in daily living described among patients at our centre after surgery. Neither the patients nor the relatives highlighted cognitive problems in the interviews.

The finding that seizure freedom led to feelings of increased autonomy was concordant with an earlier study[109]. Individuals described it as a relief that they no longer had to fear seizures and this reduced the feelings of insecurity when taking part in social activities. The relief that they no longer had to be dependent on other family members was also underlined as increasing their sense of maturity and independence. These patients and their relatives described the surgical treatment as a turning point in life, going from being sick to living a more normal life. In recent research, this process has been described after TLR, where the first five years are experienced as a stressful adjustment period followed by the development of a new sense of normality.[99]

Irrespective of seizure freedom, several patients experienced loss of energy, social withdrawal and lowered mood after FLR. Among these three entities, the loss of energy, described as mental fatigue or reduced drive to do things, was reported as common and maybe most disabling or sad for the patients as well as for the relatives. Mental fatigue is known to commonly occur in the aftermath of a neurosurgical treatment or brain injury[155, 177], but is not studied specifically after epilepsy surgery. At our epilepsy surgery centre, fatigue has been recognized for many years and we always inform patients and relatives that this is to be expected after surgery. The individual variation in symptoms is broad and it is hard to predict the degree and duration of fatigue at an individual level. Other factors like mental health, work demands, degree of social support and intellectual capacity might affect the perceived fatigue. Only a few patients in study III and IV did rate their own mental fatigue as high (one patient scored at a level of severe fatigue, three patients at a level of moderate fatigue and one patient at a level of mild fatigue) which might indicate that the reported loss of energy and social withdrawal in the FLR group is partly related to other experiences than those covered in the MFS.[155] Furthermore, patients may find it easier to describe the symptoms themselves rather than answer questions which might not correspond to what they experience. Although fatigue was experienced as elevated after surgery, our study is based on subjective reports many years later and we cannot preclude that the patients experienced fatigue preoperatively. A meta-analysis covering fatigue in epilepsy patients concluded that it is a commonly experienced phenomenon and that it is often associated with depression.[178] In our sample, only one patient scored above cut-off for depression, indicating that other factors might contribute to the perceived fatigue.

The patients and the relatives in the present study did not report symptoms related to the so called burden of normality.[106] This may be due to the long follow-up period, where most patients had their surgical treatment more than five years ago, and they may already have adjusted to the new life situation. On the other hand, the patients' experiences of reduced energy and lowered mood could also be expressions of difficulties to manage the new demands or expectations directed towards them. Since we did not use any theoretical framework in the analysis of the data, specific attention was not drawn to these tentative conclusions.

Subjective experiences of epilepsy surgery are valuable in a counselling situation as a complement to quantitative data. Being able to share other people's experiences could enhance the patient's ability to imagine what life could be like after a surgical intervention, in this case FLR. Caution must be made though, as these are subjective findings from a small sample of FLR patients and the generalizability of the results remains uncertain. Further knowledge regarding these aspects of functioning is needed and ways to reach it must be explored.

5.4 DECISION MAKING AFTER FLR

This study was the first to investigate the concept of decision making in patients after FLR. The findings were similar to what has been shown in non-operated TLE as well as in TLR samples[135-137, 139], that is, patients show a failure to learn throughout the test and, thereby, do not improve in decision-making capacity the way healthy controls do. In TLE/TLR studies, this has partly been interpreted as a result of pathology of the underlying brain structure, that is the medial temporal lobe, which could result in implicit memory deficits or dysfunction in emotional networks needed for feedback.[135] Since our study demonstrates the same tendency, in spite of generally normal memory functions and bilaterally preserved medial temporal lobes, other factors probably contribute to the difficulties found in our FLR sample.

We examined the possible association with executive functions and found moderate correlations between decision making and working memory, as well as between decision making and inhibitory control. In our study, the small sample size precluded any firm conclusions. These associations have been explored in other studies, in which different conclusions have been reached regarding the relation between executive functions (specifically working memory) and IGT performance.[137, 179, 180] One recent, comprehensive study of 20 patients with focal frontal lesions (hemorrhagic contusions, low-grade tumors, cavernomas) and a healthy control group investigated the relationship between the IGT, working memory and executive tasks and whether these cognitive processes could explain a decision-making deficit.[181] This was the first study to use an extensive battery of executive tasks with the aim to outline the associations between IGT performance and executive functions. Ten patients had dorsolateral prefrontal lesions and ten had ventromedial prefrontal lesions. Both patient groups demonstrated a failure to learn on the IGT and performed worse than controls regarding working memory, but there were no significant correlations between the two tasks, neither for the patients nor for the controls. In fact, the results showed that there was a double dissociation between IGT performance and a working memory task, that is, in both patient groups there were individuals with decline in one of the tasks, but not in the other.[181] For the other executive tasks, the results were mixed and it was concluded that the mechanisms underlying the IGT deficit differed according to the location of the lesions.[181] It is noteworthy that in our study, none of the patients were actually impaired in the working memory task (compared to standardized norms), which further underlines that the non-significant associations we found may be of less clinical value.

Although our study had a small sample size and only explored implicit decision making postoperatively, the results indicate problems that may affect daily living in patients after FLR. If patients cannot learn to interpret disadvantageous outcomes and make use of feedback in this task, would they experience the same difficulties in real life? If so, it might lead to difficulties managing social activities and work situations which need to be considered. Possibly, difficulties like these could be related to the social withdrawal and lowered mood experienced in study

III. It is known that frontal lobe lesions can lead to difficulties with social behavior and decision making.[124, 128] Whether there are similar effects following FLR is uncertain, but may be expected, to various extent, possibly dependent on resection size and localization. The small sample size in our study precluded subgroup analyses related to location of the lesions.

5.5 CONCLUDING THOUGHTS ABOUT NEUROPSYCHOLOGICAL OUTCOME AFTER FLR

In two different studies (study II and III), we explored effects on cognition, emotion and psychosocial function after FLR. Our main conclusion is that the majority of cognitive methods included cannot identify major changes in cognition after FLR. As discussed earlier, this may have several reasons. The most important reason regards the ways to measure frontal lobe functions, where existing studies (including ours) have been based on data partly collected decades ago when the neuropsychological batteries in epilepsy surgery were focused on TLR outcomes. The general knowledge regarding executive functions and social cognition was also less developed. The heterogeneity of the patient group, as well as the small sample size are other possible reasons for the non-significant findings in study II. Despite this, the results are encouraging, since the findings indicate stability regarding intellectual functions, processing speed, verbal as well as visual memory, visuospatial functions and language. In study IV we introduced methods more specific to frontal lobe functions to explore if they could identify deficits in an FLR sample, however this could only be done retrospectively.

It is interesting that neither the patients nor the relatives focused on cognitive decline in the qualitative study. Instead, they described the emotional and psychosocial changes to be more demanding. These findings are concordant with results from a long-term follow-up study after epilepsy surgery, where patients scored below standardized norms in the domains Mental Health and Social functioning in the SF-36 14 years after surgery.[100] These are aspects that are not captured by neuropsychological tests and instead need to be further investigated through a qualitative approach. The self-rating scales used in study IV could, at an individual level, partly grasp the specific frontal lobe difficulties, including increased apathy and dysexecutive behavior.[157] This indicates that such assessment techniques are good complements to neuropsychological testing. Several rating scales also have versions for relatives to fill in, which may increase the value of the results. Further development and use of tests measuring social cognition might also be a way to increase knowledge in the field.

The indication from study IV, that FLR patients had decision-making problems based on failure to learn from feedback, implies that such difficulties may arise also in daily life and affect social situations as well as work capacity. Since our study was retrospective and did not include preoperative data, it remains unknown whether the patients may have had the same difficulties preoperatively or if and to what extent the frontal lobe surgery contributed to the decision-making problems. It is noteworthy that few of the patients in study IV demonstrated clinically meaningful deficits on the metacognitive executive tasks included. The high percentage of seizure freedom in this sample may indicate a release of function regarding frontal lobe functions, which is a factor that needs to be further investigated.

Hence, an updated protocol for assessment of potential FLR candidates needs to include standardized neuropsychological tests with more focus on executive functions, self-rating scales developed with the purpose to characterize executive functioning in daily life and measures of emotional-motivational aspects of frontal lobe functions.[112] Further, decision-making tasks need to be included to outline the extent of potential problems and their relation to daily life.

5.6 PREOPERATIVE COUNSELLING IN EPILEPSY SURGERY

Throughout this thesis, the neuropsychologist's role in the preoperative counselling has been emphasized.[1] The increased knowledge about the complexity of epilepsy has led to a broader and more collaborative role for the neuropsychologist in the epilepsy surgery team, where focus has changed into a more holistic view on the patient, including cognition, emotion, expectations and social context. The predictive value of the neuropsychological assessment has also evolved as prediction models regarding cognitive functions have been developed. A thorough discussion of the results of the neuropsychological assessment should constitute a fundamental part of the preoperative counselling. This should also include a discussion of contributing factors, such as psychiatric comorbidity, and lead to a reasonable prediction about the expected cognitive outcome. The knowledge gained will help the patient to imagine or understand how a certain cognitive decline might influence family life, academic achievement, work situation and spare time activities. These are factors which may be as important to the patient as seizure outcome, and it is crucial that they are repeatedly discussed, to ensure that an informed decision about epilepsy surgery can be made.

The patients' (and the families') expectations on epilepsy surgery, is another important subject that needs to be investigated and discussed. If the patient obtains a thorough understanding of the relation between epilepsy, its' etiology, seizures and the planned surgery in the preoperative counselling, expectations can be more realistic and future disappointment or distress may be avoided.[70, 99]

In conclusion, the contribution of a neuropsychological assessment to the preoperative counselling is multifaceted and adds substantial clinical value to the medical information given. The collaborative nature of the epilepsy surgery team, consisting of neurologists, neurosurgeons, neurophysiologists, neuropsychologists and epilepsy nurses, and the information that this team could present, hopefully results in well-informed patients who are capable of making decisions which might be life-changing.

5.7 METHODOLOGICAL CONSIDERATIONS

Methodological challenges and generalizability of results

In study I, the number of patients with significant memory decline after TLR was small (n = 22), which increases the uncertainty of predictions based on the presented model. We used penalized regression in an attempt to minimize this uncertainty, but the predictive precision of the model needs to be developed by the addition of a larger number of TLR patients. Different praxes in different centres prohibit pooling of data[146] and prediction of verbal memory decline for Swedish use could thereby only be developed in Sweden, with Swedish verbal memory tests. Our intention is to keep adding data to our model, to increase its' precision. A group of patients that might not be able to benefit from the model is non-native Swedish-speaking patients, as well as patients with other mother tongues than Swedish. Unfortunately, the verbal memory test included in the model requires good familiarity with the Swedish language and assessing verbal cognition in non-native language or through an interpreter increases the uncertainty of the results.[182]

Similar challenges as described above regarding small samples are present for FLR studies when addressing neuropsychologic outcome. Even if FLR is the second most common surgical procedure, numbers are small and the resections heterogeneous.[57] Our studies, as well as other existing studies are mainly conducted on small patient samples, except for one study with 90 patients.[82] Hence, the generalizability of the results can be questioned and additional studies are needed. Ideally, multicentre studies should be conducted, with consensus regarding included measures and follow-up periods. There is an ongoing project among epilepsy surgery centres in the European Reference Network EpiCARE where neuropsychological protocols for epilepsy surgery assessments are compared, with the intention to harmonize measures. One opportunity might be to conduct an FLR study within this framework.

Repeated neuropsychological testing

Studies with repeated measurements are associated with specific challenges. One methodological problem in repeated testing is practice effects. These can vary depending on type of measure, follow-up interval, baseline level, number of repeated measurements and the use of parallel versions of tests. Modest practice effects of 1-3 points have been found in FSIQ, VIQ and PIQ[183], while one study found larger practice effects (7 points) in PIQ among healthy controls.[184] Practice effects for memory tests have been reported to be low.[175]

Another aspect to consider in repeated testing is the concept of regression towards the mean (or median), which is a statistical effect that implies that individual measurements far away from the mean of the investigated group tend to regress towards the mean at a repeated measurement.[185] This can partly be controlled for by using a control group.[186]

Test-retest reliability of the methods used, is another important issue to consider. Test-retest reliability coefficients regarding general intellectual abilities as measured by the Wechsler scales are known to be very high (0.89-0.95). The coefficients for the same abilities from our own control group, described in a previous study[74], were found to be equally high (0.92-0.97). The reliability coefficients based on the controls for speed/attention variables and verbal cognition were also high (0.79-0.98). Memory tests are reported to be more problematic regarding repeated testing and reliability.[187] In our material, the reliability coefficients for memory variables were between 0.64 and 0.88.[74] Hence, test-retest reliability was considered acceptable to good in our studies.

Defining individual change

When drawing conclusions about increase or decrease between two separate test occasions, the definition of change is crucial. One way to address this, and at the same time control for practice effects, is by using RCI. RCI values in studies I and II were calculated from the test-retest data of the controls. The method of Jacobson and Truax was used[169] and a 90% confidence interval (CI) was established. A factor for correction was added to the CI values based on the mean practice effect of the control group. Change scores exceeding the CI at the end of the distribution represent a statistically reliable change that would occur <5% of the time in the control group. Some authors advocate RCI values based on epilepsy populations rather than healthy controls[82], however very few such values have been presented and they might be affected by AED effects and other epilepsy related factors which may not be wanted. In study II, we also used Bayesian point estimate to describe how unusual individual scores were in relation to the control group. This method controls for the effect of the baseline score by including this score as a covariate during the computation.[188] It also estimates the percentage of controls that would reach a more extreme score than the one achieved by the patient. We believe that we thereby have tried to identify reliable and clinically meaningful declines and minimized the effects of chance or random measurement errors in our results.

5.8 STRENGTHS AND LIMITATIONS

The primary strengths of the studies included in this thesis encompass the well-defined cohorts, the small number of missing data and the inclusion of adequate control groups. The fact that the cohorts, due to the Swedish regional referring system, can be considered representative of the Swedish epilepsy surgery population is another strength. The inclusion of both quantitative and qualitative study designs gives a broader spectrum of results, based on both objective psychometric data and subjective experiences which complement each other. The results from this thesis thereby have a clinical value and can be implemented in the clinical setting.

One limitation of the studies is the restricted sample sizes in the quantitative FLR studies, both at group and sub-group level. The reason for this is that FLR is a less common treatment and studies are single-centre, which makes the accumulation of data very time-consuming. Furthermore, and consequently, the time periods for inclusion of the participants were long and some neuropsychological test methods were exchanged during this period, resulting in missing data for some cognitive domains. For reasons discussed earlier, adequate methods for evaluating frontal lobe functions were too few. The fact that study IV only included postoperative data precluded conclusions regarding the impact of FLR on decision-making abilities and executive functions. The discussion about the limitations is elaborated in the chapter 5.7 on Methodological considerations.

6 CONCLUSIONS

Hopefully, this thesis will contribute to an improved preoperative counselling of epilepsy patients regarding decisions about both TLR and FLR. Giving patients and relatives individualized information on the expected risk for memory decline after TLR will improve their opportunities to imagine what life would be like after surgery, and thereby enhance informed decision making. The predictors identified were side of surgery, inclusion or not of hippocampus in the resection, preoperative verbal memory function and presence of TCS in the medical history. They are easy to use in clinical practice as soon as the surgery is planned. The model showed good psychometric properties and will be a valuable tool for the neuropsychologist and the epilepsy surgery team.

Increased knowledge about cognitive, emotional and psychosocial functioning after FLR will improve the epilepsy surgery teams' capacity to discuss the trade-off of FLR with patients and families, considering that the chances of seizure freedom may be lower than for TLR. In this situation, knowing that the risk for substantial cognitive decline might be relatively low could be crucial. The two-year follow-up study in this thesis showed cognitive stability regarding intelligence, vocabulary, verbal fluency, psychomotor speed, attention, working memory, visuospatial function, verbal and visual memory and arithmetic capacity after FLR. The finding that many patients showed a decline in verbal reasoning will need to be replicated and studied further, since the reasons for the decline and its' everyday practical consequences or equivalents remain uncertain.

The qualitative study contributed with data regarding subjective experiences of life after FLR. If seizure freedom was achieved, patients as well as relatives reported increased autonomy, better capacity to experience joy and pleasure and less anxiety. Irrespective of seizure freedom, fatigue and lowered mood were described along with social withdrawal. The outcome of this study will be an important complement when counselling patients before FLR and highlight the need to include assessment of emotional-motivational functions as well as self-rating scales in the neuropsychological assessment preceding FLR. It is important to consider that decision-making difficulties can be present after FLR since it might affect the individuals' possibilities to navigate in daily life, with possibly new demands and expectations from other people, as well as from the individual him/herself. Whether such difficulties emerge as a consequence of surgery or if they are already present in candidates for FLR, needs to be clarified through prospective studies.

7 FUTURE PERSPECTIVES

The role of neuropsychology in epilepsy surgery is continuously evolving and there will be more demands on individual precision regarding prediction of cognitive outcome, as well as emotional and psychosocial consequences of different neurosurgical treatments.

Prediction models regarding other cognitive side-effects than memory decline will be requested from both patients and epilepsy surgery teams to enhance preoperative counselling. An American research group has presented a nomogram (a diagram used for calculations) to predict naming capacity after TLR[171], but so far, there are no models for the prediction of executive functions or other cognitive functions, except for memory.

Resective epilepsy surgery is an irrevocable treatment option and most patients are young. In order to make a truly informed decision about surgery, patients and families need detailed information about chances and risks, both at short and long term. As discussed earlier, the assessment protocols for FLE patients need to be adapted to measure frontal lobe functions, including executive functions, social cognition and decision-making capacity. The findings of our qualitative study of increased social withdrawal, could imply that problems with social interaction are present and this needs to be further investigated. The ILAE Neuropsychology Task Force report stated that it may take 5 years, or even longer, for quantifiable changes in HRQOL to become evident in adults after epilepsy surgery.[70] Hence, long-term studies addressing psychosocial functioning and HRQOL after FLR are also needed.

Further, more studies on decision making in epilepsy populations, and especially in FLE and FLR, are warranted. Hopefully, with larger sample sizes and with inclusion of pre- as well as postoperative data, such studies will allow for firm conclusions regarding the potential effects of FLR on decision making.

Finally, another important arena – out of the scope of this thesis, but well worth mentioning here, since it is closely related to counselling - where neuropsychological competence and knowledge is essential, is rehabilitation, or “prehabilitation”, as it is called when coping strategies are taught before surgery to facilitate postoperative adjustment to new life circumstances[189]. Future studies addressing the effects of prehabilition interventions on patients' ability to adapt to memory problems as well as to other cognitive dysfunctions would be of great value.

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