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Executive functions in children and adolescents after epilepsy surgery – analysis of long-term outcome and possible predictors

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Für meine Familie

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1. Theoretical Background

1.1. Introduction

Epilepsy surgery has been an established treatment option for refractory, focal epilepsy in children and adolescents for many decades now. Seizure freedom after surgery significantly improves quality of life of these children (Maragkos et al., 2019). However, cognitive decline is the most significant sequelae of epilepsy surgery (Baxendale et al., 2019). It is crucial to give evidence-based predictions of cognitive risks related to a potential surgery to patients and their families beforehand, so they can make an informed decision. To minimize the risk for postsurgical cognitive decline, it is also important to investigate the long-term effects of surgery on cognition. Further, it is important to broaden the knowledge about surgical effects on specific cognitive functions, which have not yet been in the focus of neuropsychological research in this field. Previous studies on cognitive development after paediatric epilepsy surgery have primarily focused on intellectual outcome, in recent years also on memory and language (Ramantani & Reuner, 2017; Gleissner et al., 2005; Puka & Smith, 2016). Except for intellectual outcome, most studies focused on the short-term post-surgical outcome, 6 months to 1 year after surgery.

In this study at hand, the research focus will be on the long-term development of executive functions after paediatric epilepsy surgery. Executive functions are crucial cognitive functions for academic achievement (Zelazo & Carlson, 2020), for self-regulatory behavior (Doebel, 2020) and for adapting to novel situations, in school and in daily life (Diamond, 2020). They have not yet been thoroughly investigated in this context.

A summary of the current state of knowledge on executive functions, paediatric epilepsy, and cognitive development in the context of paediatric epilepsy will be given, followed by the aim of this study and the research questions, before proceeding to the presentation of the study.

1.2. Executive Functions (EF)

1.2.1. Definition of EF

It is generally recognized that EF are cognitive control mechanisms, that allow adapted behavior when no preestablished schema of action is available (e.g. Lezak, 1982). The first conceptualization of EF was presented by Baddeley and Hitch (1974) almost 50 years ago when they introduced the notion of *Central Executive*. It was considered a cognitive supervisor,

controlling important memory and thought processes. Other earlier models of EF also supported the idea of a unitary mechanism, a higher order management system, responsible for attentional control and willed behavior (e.g. Norman & Shallice, 1986). Extensive research paired with the development of executive tests in clinical neuropsychology, have led to criticize this view of EF as a single executive entity, because of its lack of specificity (Packwood et al;, 2011). More informative subcomponents were proposed, with models composed of 3 or more components, mostly relying upon studies with patients with frontal lobe damage. For example, in 1982, Lezak defined the EF as the 4 following capacities: goal formulation, Planning, carrying out goal directed plans and effective performance, which were regarded necessary for socially effective and independent behavior. Disagreements did not only concern the subcomponents as well as the taxonomy used to describe EF, with terms overlapping semantically (Packwood et al., 2011). A literature review recognized 68 different names and concepts for subcomponents of EF (Packwood et al., 2011). EF has become a generic term englobing diverse cognitive functions related to controlling of thoughts, emotion and behavior (Baggetta & Alexander, 2016).

In 1972 Teuber introduced the notion of unity and diversity to describe EF as core functions, linked to the prefrontal cortex, all related by a central theme of a top down mechanism anticipating future change (as cited in Friedman & Miyake, 2017, p.2). In 2000 Miyake and colleagues proposed the unity and diversity model. Through their research on healthy college students, they identified 3 main executive functions, respectively Inhibition, updating and shifting. Confirmatory factor analysis showed that all 3 compounds were moderately correlated as well as clearly distinct. This model has been replicated since then in different age groups and is the foundation for further research in this field (i.e. Friedman & Miyake, 2017; Lehto et al., 2003). It has also been confirmed through individual difference studies, which indicate low and non-significant correlations between different executive function tasks (i.e. Lehto, 1996). However, the terminology is still inconsistent across studies. The updating function identified by Miyake and colleagues is often replaced by the more general term Working Memory in more recent works (i.e. Diamond, 2013; Blair, 2016). Blair (2016) defines EF abilities as Working Memory, inhibitory control and shifting, whereas for Diamond (2013), the 3 main EF are Working Memory (WM), inhibitory control and cognitive Flexibility.

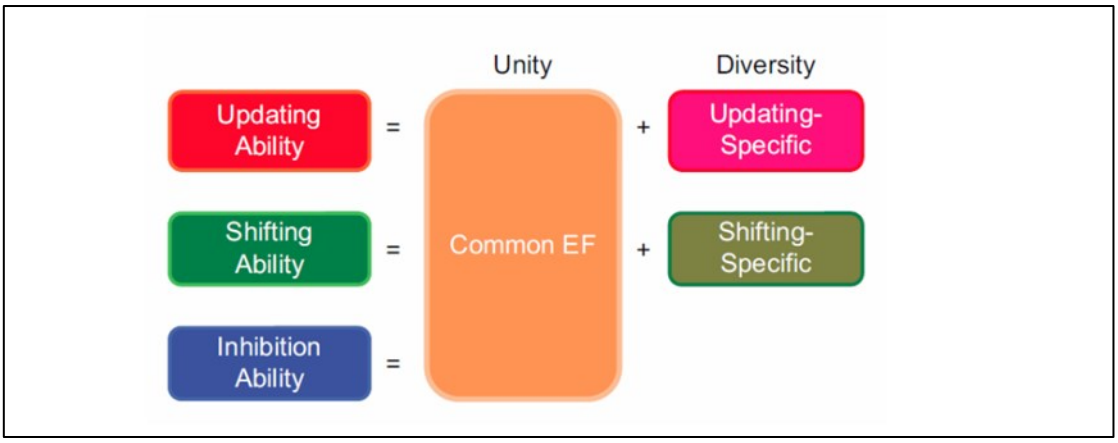

Figure 1: Schematic representation of initial (left) and revised (right) "Unity and Diversity"-model of Executive Functions

Note. Graphic retrieved from Miyake & Friedman, 2012, p.11. With the friendly pre-approved permission by Sage Journals. EF= Executive Functions.

More recently, Diamond (2020) defined EF as a group of higher cognitive processes that include the 3 main EF, as well as sustained attention, choice making and control of impulsivity, mental Flexibility such as the ability to change perspectives, consider alternatives and the ability to flexibly adjust to change, idea Fluency as well as reasoning, Problem Solving, and imagination. The author further postulates that EFs are necessary whenever new, unprecedented situations occur and when it would be unwise to follow one's instinct or intuition. EF are effortful mental processes and therefore human beings tend to reduce the demands on one's EF to a minimum.

Executive functions influence to a great extend our social behavior, our emotional regulation as well as our learning processes (Lidzba et al., 2019). Therefore, EF are crucial for academic achievement (Zelazo & Carlson, 2020). A meta-analysis with preschool and school children showed significant correlations between EF and reading and math skills (Jacob & Parkinson, 2015). Especially important for succeeding in school are goal-directed Problem Solving, flexible adaptation to change, and self-regulated learning (Zelazo & Carlson, 2020). Zelazo and Carlson (2020) propose to divide EF in "hot" and "cool" EF, which are strongly intertwined but constitute two distinct aspects of EF: "Cold" EF are cognitive EF, such as Planning, reasoning and Working Memory, whereas "hot" EF are defined by a social and emotional aspect, for example emotional regulation, theory of mind or behavioral Inhibition control. Academic outcomes are more related to cool EF, whereas poor hot EF have been shown to be related to behavior problems in school (Zelazo & Carlson, 2020). Neuropsychological testing generally evaluates cool EF, whereas hot EF intervene in the daily life, when regulation of emotions and behavior are relevant. Hence it is recommendable to complete

neuropsychological testing with standardized questionnaires about daily life (Lidzba et al., 2019).

Further, EF play an important role in neuropsychological testing of attention. For almost all attentional tasks, EF are solicited: for example, selective attention tasks demand Inhibition of irrelevant stimuli, divided attention tasks require Flexibility (Lidzba et al., 2019).

1.2.2. Neural Systems Supporting EF

Traditionally EF were equated with frontal lobe functions, because the first studies about EF were based on patients with traumatic frontal lesions leading to problems with goal-directed behavior (e.g. Luria, 1966, as cited in Friedman & Miyake, 2017, p.2). However, research on patients with various cerebral lesions undergoing functional brain imaging shows that EF are based on large neural networks, involving cortical and subcortical structures (Lidzba et al., 2019; Bettcher et al., 2016). Independently from the localization, brain lesions will lead to difficulties in EF whenever the underlying neural networks for EF are affected (Hwang et al., 2020, Anderson et al., 2010). But in adults, lesions in the frontal, especially prefrontal cortices will lead to more marked EF difficulties than lesions in other brain areas (Anderson et al., 2010). In the developing brain, the relationship between localization of lesion and EF dysfunction is less clear, lesions on any brain structure involved in neural networks supporting EF can lead to important EF deficits (Jacobs et al., 2011; Drechsler, in Drechsler et al., 2018). The dysfunction will be even more pronounced the younger the age of the child (Anderson et al., 2010).

According to lesion studies, “cold” EF deficits such as disturbances in Inhibition, Working Memory and flexiblity appear most often after lesions in the fronto-dorsolateral cortex and its connections, whereas behavior dysregulation, especially disInhibition can occur in the context of ventromedial orbitofrontal lesion (Drechsler, in Drechsler et al., 2018; Cicerone et al., 2006; Stuss, 2011). The most famous example of such behavior dysregulation in literature is Phineas Gage, who experienced a dramatic personality change with disregard for social conventions and loss of sense of responsibility in 1848, after being brain injured when a tampering iron pierced his skull while working as a construction foreman (Damasio et al., 1994). Postmortem analysis of the skull revealed probable lesions of the orbitofrontal areas of both hemispheres.

Difficulties in initiation of action and abulia are described after fronto-medial lesions and metacognitive disturbances such as anosognosia can occur in frontopolar lesions, especially of the right hemisphere (Drechsler, in Drechsler et al., 2018; Stuss, 2011).

Neuroimaging studies, using simple EF tasks, show results consistent with the existence of a common brain network for the different components of EF, supporting the unity hypothesis of a subordinate fronto-cingulo-parietal network (Niendam et al., 2012; Miller & Cohen, 2001). The prefrontal cortex and its interconnected brain regions, especially the parietal lobes and the anterior cingulate cortex are key structures for EF (i.e. Diamond, 2020; Funahashi, 2006; Takeuchi et al., 2013; Na Young Kim et al., 2017). To date, there is no consensus in taxonomy of functional human brain networks amongst research groups (Uddin, 2019). Uddin and colleagues propose the anatomical functional network name Lateral frontoparietal network (L-FPN), which supports the so-called Control network. The Control network is supposed to play a crucial role in executive functions, such as goal-directed cognition, working-memory, Inhibition and task-switching. This functional network includes mainly the lateral prefrontal cortex along the middle frontal gyrus, comprising the rostral and dorsolateral prefrontal cortex, also the anterior inferior parietal lobule, into the intraparietal sulcus, as well as the midcingulate gyrus. For Uddin and colleagues, versions of the L-FPN have been called different names in recent research literature, such as the central executive network (CEN; Sridharan et al., 2008) or the cognitive control network (CCN; Niendam et al., 2012; Miller & Cohen, 2001).

Specific analyses of subcompounds of EF showed variations in activations of cortical regions, including the anterior prefrontal cortex, the anterior and midcingulate regions, the basal ganglia, the thalamus and the cerebellum (Niendam et al., 2012), supporting the diversity aspect of the EF model by Miyake (2000). Other works suggest that, in addition to the CCN, EF also depend on collaborative functioning of intra- and interconnected networks, including the default mode network (DMN) and the salience and emotion network (SEN; Quinn et al., 2018). The DMN involves the ventromedial prefrontal cortex and posterior cingulate cortex, whereas the SEN includes the ventrolateral prefrontal cortex and anterior insula and the anterior cingulate cortex. During EF tasks, the CCN and SEN show increased activation, whereas the DMN activation decreases (Sridharan et al., 2008). This model based on functional magnetic resonance imaging studies, is known as the triple network model (Menon, 2011; Chand et al., 2017; Menon, 2019). The right fronto-insular cortex (rFIC) is also supposed to play a significant role in cognitive control, by switching between the CEN and the DMN, and thus engaging the brain's EF processes while disengaging other systems that are not task-relevant (Sridharan et al., 2008).

1.2.3. EF Subcompounds

Hereafter, the main EF as well as other EF compounds identified as frequently appearing in research (Packwood et al., 2011), are described in further detail, including underlying neuroanatomical structures and networks.

1.2.3.1. Working Memory. The construct of Working Memory (WM) has initially been introduced by Baddeley and Hitch (1974), and has been updated regularly, including, and adapting to new knowledge achieved through neuropsychological research (Baddeley, 2021). Since then, various theoretical models of WM have been proposed (Morra et al., 2018). In developmental neuropsychology, "Working Memory" and "updating" are used as synonyms (Morra et al., 2018), which is not the case in adult research. The term "Working Memory" refers to holding information in mind and mentally process that information (Morra et al., 2018; Diamond, 2020), which is critical for instance in mental calculations or for making sense of longer sentences while reading (Diamond, 2020). In the componential model of Working Memory as proposed by Baddeley (1986, cited in Baddeley, 2021), there are two subparts of WM referring to content area, the verbal and the visuospatial WM, called respectively phonological loop and visuospatial sketchpad (Baddeley, 2021; Diamond, 2020). "Updating", which is one of the 3 main EF in Miyake's model (Miyake et al., 2000), involves the ability to modify and monitor information, that is held in mind or in "Working Memory", in the light of new, incoming information (Morra et al., 2018; Lehto et al., 2003).

The dorsolateral prefrontal cortex (DLPFC) has been known to play a key role in Working Memory (Funahashi, 2006). In fMRI studies, Working Memory tasks activate the fronto-parietal pattern of the cognitive control network, as well as occipital, temporal and subcortical regions and the cerebellum (Niendam et al., 2012).

1.2.3.2. Inhibition. Inhibition involves being able to resist to external stimuli or to internal inclination to do something or to give an automatic response, and instead doing what is appropriate (Diamond, 2011; Diamond, 2020; Lehto et al., 2003). Inhibition can be dissociated in at least 2 different components (Friedman & Miyake, 2004; McAuley & White, 2011; Diamond, 2013): ***(1) Interference control*****,** also called inhibitory control in literature, has 2 subcomponents: (a) Cognitive Inhibition is the ability to resist memory intrusions from previously learned information or thoughts, that have become void (e.g. resistance to proactive interference). It also includes the ability to resist retroactive interference from items presented later. (b) Inhibitory control of attention is the ability to ignore irrelevant information at a perceptive level. Interference control is tightly linked to Working Memory, as it serves to

protect Working Memory's workspace, as it keeps irrelevant information out of WM (Diamond, 2013). The second component of Inhibition is ***(2) Response Inhibition or self-control,*** which is the ability to suppress a dominant, automatic or prepotent response. It means inhibiting one's behavior or control one's emotions, in order to resist to temptation or impulsive acting or acting prematurely. It also includes staying focused despite distractions, converging with the concept of selective attention (Diamond, 2013).

fMRI studies show that Inhibition tasks activate almost the same pattern of brain areas as Working Memory tasks, mainly the cognitive control network including the DLPFC, the anterior cingulate cortex and parietal regions, as well as to a lesser extent occipital, temporal, subcortical and cerebellar regions (Niendam et al., 2012).

1.2.3.3. Cognitive Flexibility. In 2000, Miyake and colleagues postulated that shifting was a main EF involved in shifting back and forth between multiple tasks, operations, or mental sets, through engaging and disengaging of task sets. In more recent, especially in developmental literature, cognitive Flexibility is used as a synonym for shifting and mental Flexibility (Diamond, 2020). However, cognitive Flexibility is a less specific, larger construct than shifting. Diamond (2020) describes two aspects of cognitive Flexibility: The first one is ***(1) switching*** between tasks or mindsets and point of views. The other one is quickly adjusting to change such as new demands, rules or priorities, through accommodation or through finding an alternative to reach a goal, to change approaches to problem. As Diamond (2013) points out: "There is much overlap between cognitive Flexibility and creativity, task switching and set shifting. Cognitive Flexibility is the opposite of rigidity." (p.149). ***(2) Fluency***- For Diamond (2013) Fluency tasks require mainly cognitive Flexibility. She argues that Fluency can therefore not be considered an independent EF. Common Fluency tasks are design Fluency tasks, phonological or semantic/category Fluency tasks.

A similar pattern of activation as in tasks that examined Inhibition and Working Memory, was observed in fMRI studies for Flexibility tasks (Niendam et al., 2012). Frontal and parietal regions, including the DLPFC, the cingulate gyrus as well as the superior and inferior parietal lobe, were especially activated. Additional activation was observed in other parts of the prefrontal, the occipital and temporal region.

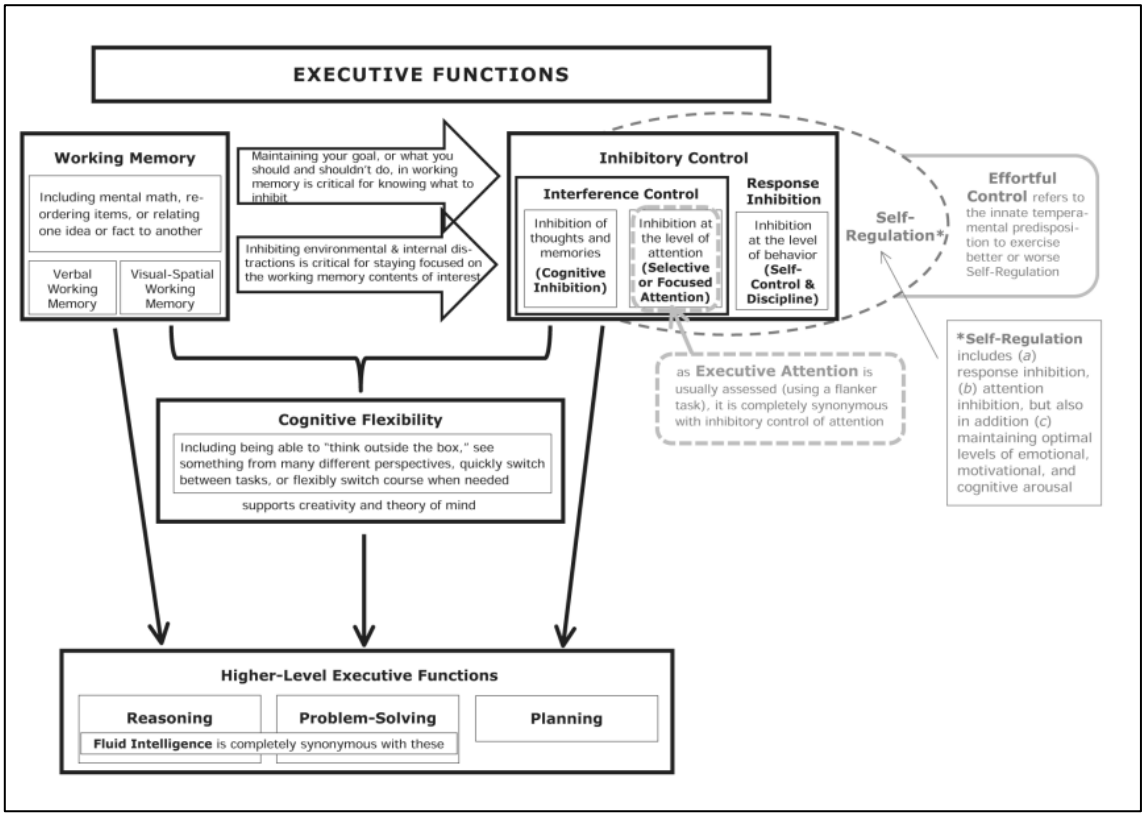

Figure 2: Executive Functions and related terms.

Note. Graphic retrieved from Diamond, 2013, p. 41. Reuse with the friendly permission of the publisher Annual Reviews.

1.2.3.4. Higher-Order Executive Functions. Diamond (2020) postulates that from the three core EFs Working Memory, inhibitory control and cognitive Flexibility, higher-order EFs are built, which are Problem Solving, Planning and reasoning (see Fig.1). Drechsler (2018) describes 9 distinct EFs without installing a hierarchy among them. She lists Inhibition, Flexibility, executive processes of WM, storage aspects of WM, as well as Planning, Problem Solving, Monitoring, activation regulation as well as regulation of emotions, motivation and social behavior. Packwood and colleagues (2011) suggest that these subcomponents of EF are not functions but task-specific behaviors, involving to various degrees the core EFs Inhibition, Working Memory and cognitive Flexibility. To date, there is no consensus or formal definition of EFs in research (e.g. Friedman et al., 2017; Packwood et al., 2011; Diamond, 2020). In the following, a selection of these EF components is presented in further detail.

Problem Solving – it means trying to reach a certain goal by finding a way to get there. To reach this goal, one needs to think critically, evaluate the problem and plan actions to solve it, then execute the plan, all while conforming to a rule set, that delimits the framework of possible actions (e.g. semantic, algebraic, logical, mechanical etc. rules; Bartley et al., 2018).

Problem Solving has been shown to involve both cognitive Flexibility and Working Memory, as well as long-term memory functions and deductive reasoning (Hopper et al., 2020).
By analyzing multiple neuroimaging studies on different problem-solving types, Bartley and colleagues (2018) were able to identify a core system underlying all types of Problem Solving: a broad network of fronto-cingulo-limbic-parietal regions, including the frontal gyri, especially the dorsal lateral and dorsal medial prefrontal cortex, anterior cingulate, parietal lobes, precuneus, occipitotemporal gyri, anterior insula, caudate, putamen and thalamus. Also, unique circuits, context-specific and depending on the nature of the problem, were identified. In summary, a complex, integrated neural system, including the salience network and the cognitive control network could be identified for Problem Solving.

Planning - also called planned Problem Solving, involves choosing between different sequences of action alternatives before acting. It is therefore very close to the concept of Problem Solving. It is a complex cognitive process, supported by the key EF Inhibition, Working Memory and Flexibility (Tecwyn et al., 2014).

Monitoring - also called response Monitoring or error Monitoring, is a function combining error detection and response adjustments after errors (Mohamed et al., 2019; Boardman et al., 2021). For some authors, Monitoring is an executive function (e.g. Drechsler et al., 2009), for others it is a "metacognition", a knowledge of our own thoughts and behavior (Boardman et al., 2021). It is a critical function for flexible adaptation to change and has been shown to be essential for learning and self-regulation (Aarts & Pourtois, 2015). Poor Monitoring can negatively impact Working Memory and response Inhibition (Mohamed et al., 2019). Its neuroanatomical basis is suggested to be located in the posterior medial frontal cortex, which is part of the cognitive control network (Mohamed et al., 2019).

Reasoning – reasoning processes are generally categorized in two types, inductive and deductive (Shin, 2019). Inductive reasoning is also called forward, because one observes different individual facts and then makes a conclusion, based on these facts. It is therefore a bottom-up approach, mostly used by novices. For a conclusion to be true, one needs to check all relevant facts. It is appropriate for exploratory measures with unstructured data. The ability needed to reason inductively is to recognize patterns and meaningful connections. Its purpose is hypothesis and theory formation (Shin, 2019; Simpson et al., 2007). Deductive reasoning, also called backward, is usually used when one is more experienced and constitutes a top-down approach. One establishes one or a set of models, which are based on general knowledge, given assumptions or principles. To verify a mental model, one needs to search for counterexamples. It is therefore goal-driven and appropriate for well-structured data and suited for classification

tasks by setting up a hypothesis and then reaching a logical conclusion by reasoning logically. Its purpose is usually the prediction of consequences (Shin, 2019).

The concepts of inductive and deductive reasoning are close to the concept of abstract reasoning. Abstract reasoning requires analysis and manipulation of information about events, objects and concepts which are not present (Solomon et al., 2011). Two types of abstract reasoning are identified: (1) Concept identification is the ability to recognize underlying category attributes and to classify. (2) Concept formation is the ability to generate schemes in order to solve a problem.

Tasks evaluating abstract reasoning, such as figural analogies and matrices, are generally used as a measure for fluid intelligence (Taylor et al., 2020). Based on a review of 37 neuroimaging studies, Jung and Haier (2007) postulate the existence of a network supporting reasoning tasks, called the Parieto-Frontal Integration Theory (P-FIT), including the dorsolateral prefrontal cortex, the inferior and superior parietal lobule, the anterior cingulate and regions withing the temporal and occipital lobes. Some white matter regions, such as the arcuate fasciculus are also supposed to be implicated.

1.2.4. Assessment of EF

Regarding EF assessment, the same EF test procedures can be applied in children as in adults, whenever norms for the younger age groups are available (Lidzba et al., 2020). Especially in younger children, where only a few measures of EF during neuropsychological testing can be retrieved, observational data during IQ testing can be very informative about problem-solving, Inhibition and Flexibility abilities (Lidzba et al., 2020).

EF behavioral manifestation in daily life can best be evaluated using questionnaires, such as the BRIEF (Drechsler & Steinhausen, 2013 for the German version). However, an extensive presentation of the behavioral aspects of EF go beyond the scope of this dissertation at hand.

An important methodological challenge arises, when researching EF. To do an EF task, generally more than one executive function is required. When evaluating EF in a neuropsychological examination with a patient, one cannot know with certainty if, for instance, a task apparently evaluating Working Memory has been failed because of problems of Working Memory or of Inhibition (Diamond, 2020). The commonly used tasks in clinical neuropsychological research to assess executive processes are impure and implicate different executive subcomponents and even non-EF cognitive processes, which complicates the interpretation of impairment on a particular task (Packwood et al., 2011; Diamond, 2020;

Miyake et al., 2000). For simplicity and comprehensive reasons, researchers often classify tasks by a single cognitive construct, for example the WCST can be described as an Inhibition task by some, and a shifting task by others (Best & Miller, 2010).A well-known Working Memory task is the backwards digit span task (Tewes, 1991), where a person must keep in mind a series of numbers and has to recite it backwards. An example of a typical task which requires Inhibition is the Stroop task (Stroop, 1935, in Lehto et al., 2003), where color words are printed in differing colors, e.g. the word "red" is written in blue ink, and the person has to name the ink color as fast as possible, and therefore has to inhibit the automated reading response. A typical and well-known task to evaluate cognitive Flexibility is the set-shifting task Wisconsin Card Sorting Test (Milner, 1964, as cited in Diamond, 2013, p.15). In this task, the participant must sort a set of cards, which can be sorted by color, shape or number. The participant has to deduce the sorting criterion from feedback given by the examiner and has to be able to switch flexibly sorting rules, whenever the examiner indicates so. In a Fluency task, the participant can be asked to name all things one can buy in a supermarket as fast as possible. Some tasks may include switching from one category to another, for instance between things one can buy at a supermarket and fruits (Aschenbrenner, 2000). Typical tasks of Problem Solving generally consist in answering novel questions by way of generating or verifying solutions. In a meta-analysis by Bartley and colleagues (2018), the list of types of problems to solve is long, including mathematical problems, verbal Problem Solving like deductive and inductive reasoning, verbal analogy problems, insight Problem Solving like riddles, also visuospatial Problem Solving like visuospatial fluid reasoning tasks, for example the Raven Matrices, visual analogy problems etc. Tower tasks, such as the Tower of London (Shallice, 1982, as cited in Teczyn et al., 2014, p. 86), are frequently used to investigate Planning abilities. In the Tower of London task, a set of three pegs with three different colored discs arranged on them (start) is presented to the participant. A different configuration of the three colored discs on pegs is presented, usually in a picture board version (goal). The aim is to rearrange the discs on the pegs, so that they match the configuration shown on the board, with the least possible moves. Inhibition is required to delay impulsive responding in favor of Planning, Working Memory is necessary to memorize the multitude of intermediate subgoals to reach a correct solution, visuospatial reasoning is also involved (Albert & Steinberg, 2011). Monitoring is usually evaluated by analyzing the errors on neuropsychological tasks: rule breaking, false positives, omissions as well as correction of errors (Drechsler et al., 2018).

1.2.5. Development of EF During Youth

EF skills are essential for flexible adaptation to changing environments and demands, goal-directed Problem Solving, adaptive social functioning and intentional learning, which are all key competencies for academic achievements and successful learning in childhood and adolescence (Zelazo & Carlson, 2020). How these EF skills develop is the subject of a growing field of research. Since the dissertation at hand focuses on EF in childhood and adolescence, the presentation of the development of EF is limited to this period of life instead of the whole life span.

1.2.5.1. Challenges- Executive function development is a topic of controversy: The finding of 3 distinct but correlated executive compounds, as presented by Miyake and colleagues (2000) in adults has been replicated in older children (e.g., 8-13 years old: Lehto et al., 2003) but the structure of executive functioning in younger children is still debated (Morra et al., 2018). Some studies propose a single factor model (e.g. Hughes et al., 2010), others distinguish two factors (e.g. Monette et al., 2015), Welsh and colleagues (1991; in Best & Miller, 2010) find the 3 factor model of Flexibility, inhibitory control and Working Memory in preschoolers. Another challenge in EF research, mentioned before, is task impurity, meaning that most EF tasks tap into multiple cognitive processes, which makes it difficult to extract valid information about one specific EF (Miyake, 2000; Diamond, 2020; Best & Miller, 2010). Related to this challenge is the fact that in developmental research, the tasks used across an age range are often not uniform: Difficult tasks are administered to older children only, or different tasks are used for younger and older children to evaluate the same EF compound (Best & Miller, 2010).

1.2.5.2. Developmental theories- In many studies, EF development during childhood and youth is conceptualized as continuous improvements in the component processes Inhibition, Working Memory and Flexibility, based on Miyake's "unity and diversity" theoretical framework (Miyake et al., 2000; e.g. Diamond et al., 2020). Also, confirmatory factor analyses in developmental studies suggest a differentiation of EF skills over the course of childhood, from a single factor model, the Common EF latent variable, to a two or three factor structure, including inhibitory control and/or cognitive Flexibility and Working Memory (Zelazo & Carlson, 2020). According to this point of view, Diamond (2013) proposes a developmental model of EF, combining the "unity and diversity model" (Miyake, 2000) and the findings of developmental cognitive neuroscience research: She postulates that Working Memory and Inhibition are main components of EF, that are functional early in life. Much later,

the third main component cognitive Flexibility/ shifting emerges from these two. The combination of all three main components then leads to the development of higher-level executive functions such as Planning and Problem-Solving (see Figure 2). These advances in EF compounds are supported by neuroimaging studies, which show a shift with age, from diffuse activity within key networks towards an increased, long-term and focal specialization of relevant networks, especially within the prefrontal cortex region (e.g. Chevalier et al., 2019).

Other developmental theories of EF have emerged since, which share the common idea that EF development is best explained as the increasing ability to resolve conflict (Best & Miller, 2010). Doebel (2020) for instance proposes an alternative to the component view by perceiving the development of EF as the emergence of skills in using control for specific goals. In this theory, development of EF is not equal with the sole development of components, but due to acquired mental content such as knowledge, beliefs, values, etc. about situations and things, that allow for better control of behavior to attain a certain goal (Doebel, 2020). On a similar note, Zelazo and colleagues (2003) postulate, that EF development emerges due to conflict between rules, that eventually become hierarchically organized.

1.2.5.3. Normal developmental trajectory of EF in childhood- Executive functions develop across the lifespan and reach a plateau during early adulthood (Lidzba et al., 2019; Best & Miller, 2010; McAuley & White, 2011). Maturing of EF compounds proceeds in nonlinear developmental spurts and is especially correlated to the development of the prefrontal lobes (Diamond, 2013; Doebel, 2020; Chevalier et al., 2019). There is evidence for hierarchical brain development, with cortical areas responsible for more basic processes such as sensory and motor regulation developing first, and cortical areas supporting more complex processes such as EF, developing second, followed by mutual influence and regulation in a top-down and bottom-up manner (Zelazo, 2020). EF development has been theorized to underlie self-regulatory behavior, essential for learning and adapting to novel situations (Doebel, 2020; Diamond, 2020).

In infancy (0-2 years), maintaining and updating representations of hidden objects in mind can be observed through visual violation of expectation paradigms in 3 ½ months old infants (Aguiar & Baillargeon, 2002). In the A-not B paradigm, 9 months old infants are able to hold in mind where a desired object has been hidden and are able to inhibit repeating to reach for a reward, when the reach would now be wrong (Hofstadter & Reznick, 1996). When using gazing rather than reaching, these advances can be observed in 5-8 months old (Cuevas & Bell, 2010). Detour reaching, which implies holding a goal in mind, planning and inhibiting a

tendency to reach straight for the goal, emerges between 6 and 12 months of age, as shown by Diamond (1988; as cited in Diamond, 2020).

In early childhood (2-5 years), significant improvements in EF happen: Children aged 2-3 years old are markedly rigid, for instance in the way they proceed to achieve a goal or in naming objects (Diamond, 2020). From 3-5 years important changes occur in EF, especially in cognitive flexibility, as expressed in social cognition (Roessler & Perner, 2016; Diamond, 2020) and on cognitive tasks that require perspective switching as in ambiguous figure tests or in tasks that require dimension switching, as in card sorting tasks (Diamond 2020; Lidzba et al., 2019). An ambiguous figure is an image, which can be perceived as two different things i.e. a duck or an old woman. Children of 3 years remain stuck in their first perception of an ambiguous figure, and even when informed about the alternative perception, cannot analyze the image from the other perspective, whereas 4-5 years old children can. In card sorting tasks, by 3 ½ -4 years children can switch from sorting by color to sorting by shape, if these properties are not shared by the same object (i.e. cards are either blue or red color cards, or cards representing a black dog or black cat; Diamond et al., 2005). Uninformed reversal, which implies efficient Inhibition, becomes possible between ages 5 and 9 (Rafetseder et al., 2021; Doebel, 2020). Around the age of 5, the visual and verbal components of Working Memory become efficient and strategic Planning abilities start to evolve (Best & Miller, 2010; Lidzba et al., 2019).

In middle childhood, between the ages of 6 and 11 further improvements in Working Memory, Inhibition, Flexibility, and Planning can be observed (Diamond, 2013). Inhibition progress is made for instance in the anti-saccade task, where one has to look the other way, as soon as a target appears. This task cannot be completed by most children of 5 years and younger. Between ages 6-7, children start to be able to control their gaze, and over the following years, speed improves to reach a plateau in the early twenties (Luna et al., 2009). Between the ages 5 and 11, children progress continually in typical Working Memory tasks such as the counting span and spatial span task (Diamond, 2013). Childrens' performance improves also in set switching Flexibility between 5 and 11 years, for instance on the Wisconsin Card Sorting Test, but adult results are not reached before the age of 15 (Huizanga & Van der Molen, 2007). Planning and organizational skills increase also significantly between ages 7 and 10. Younger children tend to use fragmented and simple strategies or instinctive reactions, whereas across the elementary school years, children use more efficient and organized strategies to reach a goal (Anderson et al., 2001; Diamond, 2013).

In adolescence, planning and organizational capacities improve furthermore, as shown for instance in the Tower of London task, where the highest performance is reached in the early twenties (Unterrainer et al., 2020). Also, speed and accuracy in task switching, as demanded in the Trail Making Test, increase, and reach its peak at 12 to 13 years of age (Arango-Lasprilla et al., 2017).

1.2.6. EF Skills for Learning Processes and Academic Achievements

A meta-analysis including studies with children ages 2 to 18 years has shown a predictive and concurrent correlation between EF skills and student achievements in reading and mathematics (Jacob & Parkinson, 2015). Even when controlling for socio-economic variables such as maternal education or IQ, EF skills in early childhood are predictors for later school achievements (Viterbori et al., 2015; Zelazo & Carlson, 2020).

Inhibition is very important for scholastic success, for instance to solve problems in mathematics, when one needs to decide whether to add or to substract (Diamond, 2013). Working Memory also plays an essential role in math Problem Solving, when one has to hold information in mind while simultaneously process new information in order to obtain a solution (Zelazo & Carlson, 2020). Working Memory intervenes in different mathematical outcomes, even when other cognitive and academic factors are considered (Raghubar et al., 2010). The central executive and the visuospatial sketchpad may be recruited more for learning and application of new math skills, whereas the phonological loop may intervene more in trained skills (Raghubar et al., 2010). Furthermore, studies showed that children with better abilities to switch a conceptual representation, such as a goal, a rule or a strategy for Problem Solving, to another one, will perform better both in math and in reading (Yeniad et al., 2013). It has been empirically shown that the different components of EF participate to different extents in reading comprehension (Butterfuss & Kendeou, 2018). For instance, updating allows readers to maintain active the relevant information in Working Memory during reading, whereas Inhibition controls the activation of irrelevant information from the text or from memory during the reading process. Shifting intervenes by integrating semantic and phonological information (Butterfuss & Kendeou, 2018).

1.2.7. Epilepsy as Risk Factor for Disturbances of EF

Executive dysfunction can occur in paediatric epilepsy patients because of the underlying epilepsy, as well as because of antiseizure medication (ASM; Lidzba et al., 2019). Epilepsy has been shown to provoke executive dysfunction in up to 58% of children with

chronic epilepsy (Reuner et al., 2016). Helmstaedter, Witt and Hoppe (2019) confirmed that ASM had a negative impact on EF, and that the effect of epileptic drug treatment on IQ was due to diminished executive functioning. ASM has been shown to negatively impact all age groups, particularly in reading attention, processing speed, and broader executive functions (Loring et al., 2004). High drug load with more than one ASM is regarded as the most relevant factor to impact cognitive performance in epilepsy patients. However, even before initiating an ASM treatment, children with new onset epilepsy have significantly more often impaired EF when compared to healthy children, especially when the etiology of their epilepsy is unclear (Reuner et al., 2016). Reilly (2011) describes disturbances in various attentional tasks, as well as in Working Memory and in Planning. Verbal Fluency is also described to be impaired (Hermann et al., 2012).

Since the dissertation at hand focuses on the development of EF in children and adolescents who undergo brain surgery for treating refractory epilepsy, after this overview of EF, the next chapter will treat the topics of epilepsy, epilepsy surgery and its impact on cognition, including EF, as well as predictors of cognitive outcome after surgery.

1.3. Epilepsy

1.3.1. Definition of Epilepsy

Epilepsy is a frequent neurological disorder, which occurs in 1-4% of the population of Western countries in their lifetime (Pérez-Carbonell et al., 2020; Perruca et al., 2018). In resource-poor countries the risk is even higher (Perucca et al., 2018). Epilepsy can appear in people of any age or ethnicity. In more than half of patients with epilepsy, seizure onset happens between birth and the age of 12 (Metz-Lutz & Majerus, 2009, in Poncelet et al., 2009). The International League Against Epilepsy (ILAE) proposed a practical clinical definition of epilepsy in 2014, which is still in use today. In this operational definition, epilepsy is a disease of the brain, which is defined by one or more of the following conditions (Fisher et al., 2014).:

1) At least two unprovoked (or reflex) seizures occurring >24 h apart.
2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3) Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the

last 10 years, with no seizure medicines for the last 5 years. Epilepsies can be classified in different subtypes, with different levels of diagnosis: seizure type, epilepsy type (focal, generalized, combined generalized and focal, unknown) and, in many cases, epilepsy syndrome (Scheffer et al., 2017). Etiologic diagnosis should be considered at every step of the epilepsy diagnosis.

In the first place, the neurologist needs to identify whether a paroxysmal event is an epileptic seizure or one of its imitators, as a myriad of differential diagnoses is possible, i.e. psychogenic non epileptic seizure, convulsive syncope, movement disorders (Fisher et al., 2017). 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" (Fisher et al., 2017, p.523). According to the ILAE, seizures can be classified in 3 main categories (Fisher et al., 2017): Focal onset, generalized onset and unknown onset. Focal onset seizures can further be classified into aware versus impaired awareness seizures, into motor onset versus nonmotor onset seizures and into focal to bilateral tonic-clonic seizures. Generalized onset seizures are either motor (tonic-clonic or other motor like clonic, tonic, atonic, myoclonic or combinations of these) or nonmotor (absence) seizures. Seizures of unknown onset are seizures where the onset was missed or obscured. These can be classified in motor (tonic-clonic, epileptic speds) or nonmotor (behavior arrest) seizures, or in unclassified seizures. After having classified the seizure type(s) occurring in one patient, the second level 'epilepsy type', must be determined. Many epilepsies will include a variety of seizure types. Interictal and/or ictal EEG findings will support clinical diagnosis. Imaging studies, mostly MRI, will bring important information to find the underlying etiology. Epilepsy types can be categorized into 4 groups, according to the ILAE (Scheffer et al., 2017): Focal, generalized, combined generalized and focal, and unknown epilepsy. Focal epilepsies are epilepsies with focal onset seizures, or with multifocal epileptiform discharges and with seizures involving one hemisphere. The third level of classification is the epilepsy syndrome diagnosis, which is defined as "a cluster of features incorporating seizure types, EEG, and imaging features that tend to occur together" (Scheffer et al., 2007, p. 515). Furthermore, it often has specific comorbidities such as intellectual disability or psychiatric symptoms, as well as distinct findings in imaging studies or on EEG, specific seizure triggers and age-related onset and progression (Wirrell et al., 2022). An epilepsy syndrome diagnosis does not correspond to one etiology, even though some etiologies are associated with certain epilepsy syndromes. For example, the phenotype of a genetic mutation can differ and result in different epilepsy syndromes: Dravet syndrome is linked in more than 80% of patients to a pathogenic

variant of *SCN1A*. However, *SCN1A* mutations can also be associated with Genetic Epilepsy with Febrile Seizures Plus (GEFS+).

1.3.2. Epilepsy Therapy

Pharmacological therapy with antiseizure medications (ASMs) is the first-line therapy for epilepsy. Its goal is to suppress seizures, all while minimizing drug toxicity, and to obtain the best possible quality of life (Perruca et al., 2018). Usually, treatment with a single ASM is started after the epilepsy diagnosis has been made. ASM selection depends on the patient's characteristics, for example gender or age, and the seizure types. More than 50% of patients become seizure free with a minimal to medium dose of their first ASM. When seizures persist despite up-titration to the highest tolerated dose, diagnosis should be revised, and treatment adherence should be checked. If switching to another ASM in monotherapy is needed, there is only 15% chance of attaining seizure freedom with the new medication. After two to three trials of monotherapies, polytherapy, combining two or more ASMs, should be considered. Less than 15% of patients who continue to have seizures after the use of two appropriate ASM trials, become seizure-free with other ASMs (Perucca et al., 2018). Therefore, the ILAE has defined drug resistance by a failure of adequate trials of two tolerated, appropriately chosen ASM schedules, as monotherapies or in combination, to achieve seizure freedom (Kwan et al., 2010). When drug resistance is present in patients with focal epilepsy, presurgical evaluation should be performed (Bast et al., in Arzimanoglou et al., 2016). In presence of focal, multifocal or monohemispheric seizures, presurgical work-up should apply to patients who show a clear lesion on MRI as well as in MRI-negative patients. Surgical therapy consists mostly in resecting, sometimes in disconnecting or destroying the epileptogenic brain tissue (Perucca et al., 2018).

If surgery is not an option, further ASM trials should be offered. However, even the introduction of second-generation ASMs hasn't improved the probability of seizure-freedom and approximately one third of epilepsy patients remain pharmaco-resistant. Nonetheless, these new ASM are globally better tolerated with less negative side effects.

A few non-pharmacological therapies exist, with variable success in treating seizures: A recent review by L. Pérez-Carbonell and colleagues (2020) reported that the vagus nerve stimulation (VNS) via implantation of a stimulator, which has been in use for 25 years, has shown to reduce seizures by 50% in frequency in 26-40% of patients within a year. Transcutaneous VNS is a more recent form of stimulation and has the advantage that invasive

procedure is not needed. Another frequently used treatment option is Ketogenic diet, which has been introduced in 1924 in the Mayo Clinic in the USA (Wells et al., 2020).

1.3.3. Neuropsychological Consequences of Epilepsy in the Paediatric Population

The causes of the multitude of possible neuropsychological deficits in children with epilepsy are multifactorial: The age at onset, the epilepsy syndrome, the seizure type and frequency, the underlying cause of epilepsy and the intensity of the therapy, as well as the psychosocial environment can have a negative impact on cognition (Danguecan & Smith, 2019). Static factors like a metabolic or genetic disposition or a brain lesion is usually linked to permanent neuropsychological impairments, whereas the impact of more fluctuating factors like ASM treatment, seizure frequency or psychosocial aspects can vary over time (Lidzba et al., 2019). Normal cognitive profiles exist, usually in treatment responsive and uncomplicated epilepsies. But isolated deficits or global impairment are also frequent in children with epilepsy (Van Itterson et al., 2014, Lidzba et al., 2019). A brief presentation of neuropsychological deficits occurring in children with epilepsy will be given, whilst skipping EF. For more information on deficits in EF in this population, one can refer to chapter 1.1.7.

Regarding general IQ, intellectual disability (IQ below 70) is present in up to 73% of children with metabolic/structural epilepsies, whereas it occurs in about 22% of children with genetic or unknown causes of epilepsy (Lidzba et al., 2019). The mean IQ of children with epilepsy confounded is about 10 standard points lower than their healthy, age-matched peers (Dodson, 2002), in surgical candidates the mean IQ is even lower, 15 points below the norm and severe developmental impairment is more frequent (Ramantani et al., 2018b). Especially children with treatment refractory epilepsy or with structural and metabolic epilepsy show important difficulties in academic achievement (Reuner, 2018). ADHD is diagnosed in up to 17% of children with epilepsy, which is much more frequent than in the normal population. Furthermore, children with epilepsy tend to have either the inattentive or the mixed type, more than the usually predominant hyperactive type of ADHD. Another particularity of this population is a well- balanced gender distribution of ADHD, whereas in the normal population, boys are more frequently diagnosed (Reilly, 2011). In children with temporal lobe epilepsy (TLE) memory deficits are very common, occurring in up to 80% of the children (Rzezak et al., 2014; Smith, 2016). Ongoing seizures emerging from the temporal lobe lead to developmental hindrance of memory capacities, with persisting reduced learning and long-term memory abilities starting in childhood years (Helmstaedter & Elger, 2009), Children with frontal lobe epilepsy (FLE) also often demonstrate memory deficits, how these can be distinguished from

memory deficits seen in TLE is still a subject for debate (Kibby et al., 2019; Smith, 2016). Language deficits occur especially in temporal, less frequently in frontal lobe epilepsies of the left hemisphere. If the epilepsy starts early, in 30% of these cases the language representation is atypical, with language comprehension and production re-localizing in the right hemisphere (for more details see chapter 1.3.2). This can lead to the *crowding* effect, with difficulties in naming and visuo-spatial capacities due to lack of space in the right hemisphere (Lidzba et al., 2019; Danguecan & Smith, 2019). Furthermore, a meta-analysis revealed poor lexical retrieval capacities and verbal Fluency deficits in children with epilepsy, independently of their epilepsy type (Bailey & Im-Bolter, 2021).

1.4. Cognitive Development in Paediatric Epilepsy Surgery

1.4.1. Importance of Paediatric Epilepsy Surgery

Epilepsy surgery is an established treatment for refractory, focal epilepsy in children and has been performed as early as 1938, with McKenzie performing the first hemispherectomy for seizures (McKenzie, 1938, as cited in Arzimanoglou et al., 2016, p.XIX). Advances in structural and functional neuroimaging as well as the high rate of psychosocial morbidity in adults with long-term epilepsy led to assess possible candidates for resective surgery earlier in their clinical course since the 1970s. Today, epilepsy surgery is effective over a wide age range for a multitude of etiologies and clinical presentations (Arzimanoglou et al., 2016). To minimize the psychosocial and cognitive risk linked to refractory epilepsy and to improve the quality of life, referral for presurgical evaluation should be done as early as possible (Cross et al., 2006). The risk/benefit ratio has to be taken into account, whilst considering the brain plasticity of the child. Especially children with epileptic encephalopathies, characterized by behavioral changes, a stagnant or regressive cognitive development and almost continuous EEG abnormalities should be referred promptly, since recovery is possible to some extent in the early course (Ramantani & Reuner, 2018). Discussions often arise as to whether drug resistance should be demonstrated before proceeding to surgery in cases, where surgical intervention is considered the best option. The ILAE insists on proving drug resistance before surgery (Kwan et al., 2010). However, no time course is specified, so treatment in i.e. younger children with multiple ASMs over a short period of time is possible to fulfill the drug resistance criteria.

Long-term recurrent seizures can have a negative impact on brain development, especially in the presence of epileptic encephalopathy. Studies showed improvement in the short and in the long-term, for example in IQ, when seizures stopped after surgery (Freitag &

Tuxhorn, 2005). Improvement of cognitive outcome in the long-term seems to be related particularly to the withdrawal of antiseizure medication (Skirrow et al., 2011).

Quality of life is improved through seizure freedom after surgery, especially because of lower rates of anxiety and depression symptoms (Puka & Smith, 2015). Seizure free children after surgery have a significantly better quality of life than before surgery and a higher quality of life than matched medically treated controls (Maragkos et al., 2019). Long-term outcome data shows that 11-30 years after paediatric epilepsy surgery, seizures are significantly controlled in 75% of paediatric patients, 63% of the patients are Engel class 1A outcome, so completely seizure free and 54% are cured of epilepsy, which means they are seizure free and off antiseizure medication. Surgical complication rates are reasonable with an estimation of 9% (Hoppe et al., 2022). Altogether it is evident, that an early surgical intervention for intractable epilepsy in children is critical.

1.4.2. The Role of Neuropsychological Assessment in Perisurgical Evaluation

Minimal requirements for presurgical evaluation in paediatric patients who are candidates for epilepsy surgery include detailed history taking and description of paroxysmal events, a thorough neurological examination, at least an interictal scalp EEG, preferably a video-EEG recording of seizures, high resolution magnetic resonance imaging (MRI) with a specific epilepsy protocol, as well as a neuropsychological assessment (Arzimanoglou et al., 2016; Gaillard et al., 2020). If possible, the psychologist should associate the standardized measures of cognitive functioning to measures of behavioral and psychosocial functioning to have a comprehensive overview of the patient (Baxendale et al., 2019). The different results should then be presented and discussed in a pluridisciplinary case conference, in which the decision to recommend or not an appropriate surgical procedure will be taken (Wyllie & Najm, 2016).

According to the ILAE Neuropsychology Task Force Diagnostic Methods Commission (2017-2021), neuropsychological presurgical work up has 4 purposes: First to establish a baseline for postsurgical outcome comparison; second, to contribute to seizure lateralization, localization and characterization; third, to give evidence-based predictions of cognitive risk related to the proposed surgery, including amnesic risk and psychosocial outcome, since cognitive decline is the most significant sequelae of epilepsy surgery; and forth to obtain the evidence base needed for comprehensive preoperative counselling, explaining neuropsychological test results and implications (Baxendale et al., 2019).

Repeated, long-term assessment of neuropsychological changes following epilepsy surgery is recommended to be an integral part of postsurgical follow-up, as postoperative

cognitive functioning is dynamic. The ILAE Neuropsychological Task Force recommends at least one postsurgical neuropsychological evaluation 6-12 months after surgery. Up to six months after surgery, acute effects of surgery such as oedema and Wallerian degeneration can impact the neuropsychological profile. One year after surgery, gradual improvement of cognition will plateau, but great inter- and intraindividual differences occur often (Engman et al., 2006). Children recover faster and improve more than adults after surgery, which speaks for greater plasticity and compensational capacity in childhood (Gleissner et al., 2005; de Knegt et al., 2020). Postsurgical seizure control and drug load play an important role in cognitive outcome and need to be taken into account in neuropsychological profile interpretation (Baxendale et al., 2019). Timing of these repeated assessments need careful Planning as practice effects can contaminate the results, parallel test forms should be used whenever available. Important changes in health-related quality of life, mood and social adjustment can occur after more than 5 years post-surgery (Coleman et al., 2019), but it is beyond the scope of this dissertation at hand to provide a full review of these important psychosocial issues.

1.4.3. Challenges for Cognitive Development in Paediatric Epilepsy Surgery

A brief overview of what is meant by plasticity, as well as by vulnerability is following and will give clarity. It is accompanied by more precise information on the development of neuropsychological functions within the framework of brain injury and epilepsy surgery.

1.4.3.1. Plasticity: Plasticity in the developing brain is the capacity of the brain to be formed by experience through learning and remembering, as well as to recover and reorganize after injury (Gleissner et al., 2005). In the first two years of life, synapses are abundantly formed in the brain **(*blooming*)**. Through experience, the most useful synapses are selected and myelinated to enhance communication throughout the brain **(*pruning*)**. This process explains the impressive learning capacity in babies and toddlers and forms the basis for greater compensation in the developing brain in case of injury than in the adult brain (Lidzba et al. 2019). The highly debated ***Kennard Principle*** postulates that "if you have a brain lesion, have it early". It is based on the works of Margaret Kennard in experimental animal research and shows greater recovery in the very young than in adults after unilateral motor cortex lesions, as a result of greater plasticity in the immature brain (Kennard,1942; Gleissner et al., 2005). On a same note, a left sided stroke in adults results most often in long-lasting aphasia and right hemiplegia. In early childhood the same injury results in right sided cerebral palsy, but the language prognosis is much better, with almost normal language development after a brief delay, when the homologous areas on the right hemisphere are functional (Gleissner et al.,

2005). This ***reorganization*** appears only in the very young, immature brain, when a function can be relocated in other intact brain areas. Usually the function relocates at the same brain location on the opposite hemisphere- this process is called ***interhemispheric reorganization*****.** ***Perilesional reorganization*** can also occur in older children and adults, resulting mostly in a regained but more impaired function (Lidzba et al., 2019). This reorganization process of annexing functions of damaged brain areas to areas which were not involved in these functions before is also called ***reconstitution*** (Helmstaedter & Elger, 1998). When plasticity is not possible, i.e. because critical periods of development are over, behavioral compensation techniques and strategies to overcome impairment, called ***compensation and substitution***, can come into effect (Helmstaedter & Elger, 1998). For instance, short-term memory is strongly related to attention and verbal capacities. A patient with temporal lobe epilepsy and short-term memory impairment but good attentional and verbal functions can compensate behaviorally by using these (Helmstaedter & Elger, 2009). In regard of epilepsy surgery, brain development extends until puberty and enables children and adolescents to regain more function post-operatively than adults, for instance in general IQ or in memory tasks (Gleissner et al., 2005; Smith et al., 2011).

1.4.3.2. vulnerability: Compensation mechanisms such as interhemispheric reorganization for language is only possible when the lesion appears early in life and is limited to one hemisphere. If both hemispheres are injured, interhemispheric reorganization is not possible. Furthermore, early diffuse, bilateral brain lesions lead to more severe cognitive impairments the earlier they appear in life. This is due to large network dysfunctions, leading on the long-term to impacted development of complex cognitive functions like attention and executive functions **(*growing into deficit*).** In the same way, if a basic cognitive function is impaired early in life, connected and later emerging complex cognitive functions will also be impacted on the long run (Lidzba et al., 2019). Regarding epilepsy, the developing brain is especially vulnerable to the negative influence of recurring seizures. It has been shown for different patient groups, for instance children with stroke or brain tumors, that the concurrent presence of seizures negatively impacts their overall cognitive development (Greenham et al., 2017; Lidzba et al., 2019; Vargha-Kadem et al., 1992). It is hypothesized that epileptic activity mixes up the synaptic selection principle by blurring the meaningful neuronal activity with meaningless epileptic activity (Gleissner et al., 2005).

1.4.3.3. Plasticity and vulnerability in the context of epilepsy surgery: Epilepsy, as well as surgery, influence the maturing brain. The neurodevelopment is still ongoing at the time of surgery (Smith & Berl, in Arzimanoglou et al., 2016; Pohlman-Eden et al., 2015).

Hemispheric specialization of function, such as handedness, language and memory predominance emerge during development at different periods and can therefore be greatly impacted through epilepsy and surgery.

For language representation, adult-typical dominance of a hemisphere, generally left dominance, emerges from an early bilateral language network and evolves during childhood and adolescence (Kadis et al., 2010). The potential for interhemispheric plasticity following early large, left hemisphere injury or resective surgery, resulting in bilateral or right sided hemispheric language dominance decreases around the age of 5 or 6 (Kadis et al., 2010; Hertz-Pannier et al., 2002). Ipsilateral shifts from the damaged primary language area to adjacent areas has been demonstrated, but with very reduced language capacities (Helmstaedter & Elger, 1998). This must be considered when taking the decision for epilepsy surgery in language eloquent areas, because language capacities need to be preserved imperatively.

Memory laterality becomes evident in adolescence, with verbal memory performances being usually based on the integrity of the left mesial and lateral temporal lobes, and typical adult-like deficit patterns following temporal resections appear (Helmstaedter & Elger, 2009; Law et al., 2017). In younger children with frontal or temporal lobe epilepsies, cognitive impairments in memory and executive functions can largely overlap, impeding the search for lateralizing or localizing signs in the presurgical context (Smith, 2016; Rzezak et al., 2014).

Hand-use preference for fine motor tasks, also known as handedness, is also predominantly associated with the left hemisphere and emerges during the 8th and 24th month of life (Ferre et al., 2020). To a lesser extent than language representation, motor functions can relocalize after early brain injury, which opens possibilities for functional plasticity after surgery (Staudt, 2010).

Early brain lesion and early onset of seizures in either hemisphere can affect the development of these functions or lead to atypical representation. It is of utmost importance to take into consideration all of these possibilities for plasticity and vulnerability when Planning a surgical intervention for epilepsy in children and adolescents (Baxendale et al., 2019).

1.4.4. Seizure Outcome After Paediatric Epilepsy Surgery

The Engel Epilepsy Surgery Outcome Scale is the most used seizure frequency metric (Chisolm et al., 2022). Class I is defined as being free of disabling seizures, with class Ia being completely seizure free since surgery, class Ib having only nondisabling simple partial seizures, class Ic having some disabling seizures after surgery but free of disabling seizures for at least 2 years and Id having generalized convulsions with ASM discontinuation only. Class II

corresponds to having rare disabling seizures, class III to showing worthwhile improvement either through seizure reduction or through prolonged seizure-free intervals, and class IV is defined as showing no worthwhile improvement in seizure intensity and frequency since surgery (Engel et al., 1993; Appendix 1). In most studies, Engel Class I is used to classify patients as being "seizure free", even though this is only completely true for Class Ia. Classes Ib, c, and d are free of disabling seizures but still experience epileptic seizures (Chisolm et al., 2022).

A systematic review and meta-analysis of 258 studies on paediatric epilepsy surgery showed seizure freedom in 64.8% of patients 1 year after surgery (Widjaja et al., 2020). Seizure freedom declines progressively to 60.3% at 5 years and to 39.7% at 10 years follow-up. Highest seizure freedom was observed in hemispheric surgery, followed by temporal and extratemporal lobe surgery. Tumor patients had higher rates of seizure freedom than patients with malformations of cortical development. Seizure freedom was higher for lesional epilepsies and for complete resections, than for non lesional epilepsies and incomplete resections. In an ILAE paediatric surgery task force report from 2008, 20% of patients in paediatric epilepsy surgery cohorts undergo extratemporal resections, 36% of intralobar surgeries in children are frontal lobe resections and about 10% concern resections in the parietal and occipital lobe. In both of these interlobar groups, about 60-66% are seizure-free after surgery in the long-term follow-up (1.5 to 18 years), 30% remain seizure free after ASM discontinuation (Harvey et al., 2008; Ramantani et al., 2017). Predictors for seizure freedom were a shorter epilepsy duration, lesional epilepsy and the absence of generalized seizures before surgery (Englot et al., 2013). Full resections of the epileptogenic lesion are also a determining predictor of seizure freedom (Ramantani et al., 2018b).

1.4.5. Pathophysiology of Cognitive Outcome

For decades, possible surgical cognitive outcome has interested neuropsychologists, initially in the context of mesiotemporal lobe surgery. The `functional adequacy hypothesis´ of hippocampal function in this context has been modelized (Penfield & Milner, 1958; Chelune, 1995) but has since been used to explain various cognitive deficits occurring after resective epilepsy surgery (Moosa & Wyllie, 2017; Kaur et al., 2022; Helmstaedter & Elger, 1998). The `functional adequacy hypothesis´ states that preoperative cognitive functioning is related to the intrinsic abilities of the tissue to be resected, therefore a better presurgical cognitive level bears a higher risk of postsurgical decline. The other major model for postsurgical outcome discussed by Chelune (1995) is the `functional reserve hypothesis´, which supports the idea of a

preservation of function when the unoperated side shows good presurgical functioning and takes over the functions of the operated site. Recent neuropsychological studies seem to confirm, that postsurgical cognitive outcome is an interplay of both models, an interaction of presurgical function inside the surgical zone and of presurgical function outside of the surgical site, especially the contralateral, homologous site in the case of language and memory (Moosa & Wyllie, 2017; Helmstaedter et al., 2020, Puka et al., 2017). For instance, studies have found that a high presurgical cognitive level was a risk factor for postsurgical decline, but simultaneously it was a predictor of better postsurgical cognitive overall outcome (Puka et al., 2017).

In 2017, Moosa and Wyllie generalized both models to explain how cognitive change can occur after epilepsy surgery, and how the understanding of the underlying pathophysiology can minimize the risk of loss of function: The epileptologist needs to identify the *epileptogenic zone* to determine the region of the brain where surgery will be performed. It is a hypothetical zone which is indispensable for the generation of epileptic seizures, and which needs to be removed to become seizure free. In and around the epileptogenic zone is the *functional deficit zone* – it refers to the zone of dysfunction caused by the epileptic activity and can be identified through various tests like neurological examination, slowing on EEG, hypometabolism on positron emission tomography scan and neuropsychological evaluation. In some cases, function in regions remote from the epileptogenic zone but connected to it might be altered, especially in children with epileptic encephalopathy involving large brain networks. Cognitive outcome after surgery is the result of an interplay of 1) function inside the epileptic zone and 2) dysfunction outside the epileptic zone. Following this logic, 3 main post-surgical outcomes are possible: unchanged, improved and worsened cognition. Unchanged cognitive performance after surgical removal of the epileptic zone occurs in patients in which the epileptic and the functional deficit zone overlap, and the epileptic zone doesn't carry critical cognitive functions. Improved cognition is expected in patients in which prior to surgery, the functional deficit zone largely extends the epileptogenic zone, such as it is the case for epileptic encephalopathies due to focal lesions. In this case, the removal of the epileptogenic zone enables the "release" of abilities located in the rest of the functional deficit zone. Cognitive decline occurs when the epileptogenic zone is part of eloquent cortex, which means it harbors functional brain tissues responsible for an essential cognitive function such as language or memory, and the dysfunction outside the epileptogenic zone is minimal. However, if the seizure burden is so high that the quality of life is massively impacted, cognitive decline may be acceptable in exchange for seizure reduction or freedom after surgery.

The appropriate timing of surgical intervention is very important, since it is one of the only modifiable outcome predictors. To avoid irremediable brain damage due to intractable seizures and ASM on the developing, immature brain, a short latency to surgery is of great importance. Moreover, reorganization and plasticity are higher at that very young age, allowing for complete resections of entire epileptogenic zones, with less hesitation when surgery is close to eloquent areas, as in older patients (Ramantani et al., 2018b).

1.4.6. Cognitive Outcome After Paediatric Epilepsy Surgery

1.4.6.1. Possible Cognitive Outcomes. On an individual level, 5 major long-term neuropsychological outcome possibilities exist (Smith et al., in Helmstaetter et al., 2011; Baldeweg & Skirrow, 2015). First, the cognitive development is unchanged, the surgery did not influence the developmental course. Second, cognitive "catch-up" is possible when seizure freedom allows brain maturation and therefore cognitive improvement in paediatric patients. Third, surgery related cognitive impairment appears due to removal of functionally intact brain tissue. These 3 possibilities correspond to those formulated by Moosa and Willie (2017). Following Smith (2011) as well as Baldeweg and Skirrow (2015), 2 other possible developmental outcomes exist: Forth, the development is slowing. Preoperatively the functional level of the child decreased with ongoing seizures, the surgery stopped the cognitive decline, but the child develops slower than healthy peers. Fifth, "growing into deficit" emerges in the postsurgical longitudinal course, when supposedly new cognitive deficits occur in late emerging skills and functions as children progress into adulthood (for instance evaluation of episodic memory starting at the age of 5 or 6 years of age reveals memory deficits in young school aged children, which were not detectable before; Moosa & Willey, 2017).

1.4.6.2. Postsurgical cognitive outcome in other studies. Most children who are epilepsy surgery candidates, present a delay in neurodevelopment due to the underlying, epileptogenic pathology. The goal of epilepsy surgery, besides stopping seizures, is improved developmental capacities. In a lot of these young patients, a downhill course of epileptic encephalopathy, which is the progressive mental developmental delay due to epileptic activity, is frequently ongoing. Surgery is the only option left to stop the progression and enable further cognitive development. Status of cognitive functioning is a major determinant of quality of life in children with epilepsy, therefore the best possible cognitive outcome needs to be a goal of surgery, next to seizure freedom (Mikati et al., 2010).

Regarding **intellectual functioning,** pooled results of 16 studies showed 19% improvement of IQ (increase of 8-15 IQ points or 1 standard deviation or change to a higher

developmental category), 11% showed cognitive deterioration after surgery and 70% showed no change in IQ after epilepsy surgery (Van Schoenefeld & Braun, 2013). In most paediatric studies, overall cognitive development is stable after surgery, however on individual level, postsurgical increases or losses are possible (Ramantani & Reuner, 2018; Ramantani et al., 2018b; Kaur et al., 2022). Improvement is more often observed in patients with severe impairment, than in patients with high cognitive functioning. Improvements tend to appear later in the postsurgical course, often measured only at the 5 years postsurgical follow-up assessment or later and in subgroups, such as in temporal lobectomy patients (Skirrow et al., 2011). In the short-term 1 year follow up, gains in IQ can be observed in individual patients, following the cessation of intense bilateral propagation of epileptic activity (Roulez-Perez et al., 2010). Therefore "Catch-up" of cognitive development with increased overall IQ should be considered a "bonus" after paediatric epilepsy surgery. Irreversible damage to neural networks through epileptic encephalopathy as well reorganizational, plastic processes including crowding effects after removal of the epileptogenic area and the loss of retained function in this area may all contribute to the lack of increased performance in most cases (Roulez-Perez et al., 2010). Furthermore, a stable postsurgical IQ is not only corresponding to absence of deterioration but can be considered a success in cognitive development in many patients, who showed a presurgical cognitive ongoing decline (Ramantani & Reuner, 2018). In conclusion, most studies up to date have not found significant group changes in IQ post-surgery, and if they found significant changes, those were generally small in magnitude. In current clinical practice, most research examined short-term outcomes of 1 to 2 years after epilepsy surgery and there is still insufficient evidence on long-term cognitive outcomes (5 years and longer post-surgery) (Smith & Baldeweg, 2017; Kaur et al., 2022).

Post-operative changes for circumscribed cognitive functions have mostly been investigated for verbal learning and memory, as well as for language performance. Study results are often contradicting, especially regarding **memory functions**: In a seminal study by Gleissner and colleagues (2005) verbal learning is reduced after temporal surgery in children and adults, however children recover 9 months after surgery. In another study, paediatric temporal lobe surgery patients showed non-material specific declines in memory performance even one year after surgery, whereas frontal lobe surgery patients showed memory improvements (Martin et al., 2016). In a paediatric epilepsy surgery cohort study, short-term verbal memory and visual learning scores increased significantly 2 years after surgery in the surgical group but not in the control group of surgical candidates (Sibilia et al., 2017).

However, some study results did not reveal improvements, mostly showing overall low memory scores compared to healthy children with no change after surgery. In a paediatric surgical cohort with different surgical localizations, visual memory after surgery was mostly unchanged and even below expectancy in 18% of patients when using the empirically based SRB analysis (Meekes et al., 2014). There were no associations of clinical variables such as side and site of surgery or postsurgical seizure freedom with memory outcome. In another cohort of paediatric epilepsy surgery patients combining temporal, extratemporal, uni- and multilobar lesionectomies, no changes over time in everyday memory and on memory tests were observed, no specific changes in the surgery group and no benefit from seizure freedom could be noted. All children with epilepsy, surgical or not confounded, had memory difficulties in comparison with the healthy control group (Oitment et al., 2013). Puka and Smith (2016) evaluated memory outcome in a cohort of surgical and non-surgical patients at baseline and 4 to 11 years after. No improvement on group level over time was found. Memory outcomes were independent of surgical status. Seizure free patients were better than others at story recall both at baseline and at follow-up, without showing improvement. Patients with extratemporal surgery showed postsurgical declines in word list recalls, but not in recalls of stories or paired words, suggesting an impairment in effortful retrieval or organizing information, since in stories and pairs, the recall is facilitated by meaning or cues. Despite improvements in IQ over time, memory capacities did not increase, indicating that change in memory is not only explained by change in IQ. Furthermore, improvements on an individual level were associated with low baseline memory scores, maybe because of an accelerated development after a period of stagnation or regression due to epilepsy.

Regarding **language outcome**, few studies exist on this topic. In a long-term follow-up study, Puka and Smith (2016) showed improved language performance in seizure free children and in children with significantly shorter epilepsy duration, with a trend for decline in other groups. Also, children with surgery on the non-dominant side for language had higher scores in naming before and after surgery. Smith and colleagues (2014) found a significant positive effect of time for vocabulary in both the seizure free and in the seizure recurrence group more than 7 years after surgery.

Regarding other neuropsychological functions like **attention, visuospatial skills and especially executive functions (EF)**: EF is the most frequently impaired cognitive function in presurgical epilepsy patients (i.e. Operto et al., 2020; Ray et al., 2015). Kaur et al. (2022) found more individual declines than improvements on measures of executive functions and visuospatial skills post-surgically, except for Working Memory, which had a higher proportion

of postsurgical improvers. Processing speed and attention also improved. Ueda and colleagues also found improved focused attention skills after surgery (2021). Sherman and colleagues (2011) found mostly improved verbal Fluency in surgery patients of various age, Vega and colleagues did not find significant changes post-surgically in verbal fluence in paediatric patients (2015). Mental Flexibility was generally unchanged after temporal lobe surgery. In a case study, white matter lesion due to resection on the left supplementary motor area caused serious and lasting EF dysfunction with impulsivity, distractibility and verbal Fluency difficulties (Endo et al., 2014). Some studies find a relationship between postsurgical improvement of cognitive functions, especially EF, and a better seizure outcome and/or a reduced ASM load (Hallböök et al., 2013; Puka et al. 2017; Puka & Smith, 2016), while others have not (Lendt et al., 2002; Skirrow et al., 2019). However, several studies suggest that improvements due to seizure and medication reduction may need years to manifest (Puka et al., 2017; Skirrow et al., 2019; Kaur et al., 2022). More details on circumscribed cognitive functions results are given in the following chapters, especially in 1.5.5. Localization of surgery.

Using formal IQ and neuropsychological testing to depict real life improvement of cognitive skills has limitations. In clinical practice, significant improvement in social skills, behavior and attention is often reported by families in the years after surgery, despite no significant change in cognitive testing (Moosa & Willey, 2017; Ramantani & Reuner, 2018). Furthermore, significant positive changes in IQ test results are often delayed by years, highlighting the importance of long-term follow-up evaluations (Moosa & Willey, 2017; Puka et al., 2017). The cognitive outcome in surgical patients as perceived by parents shows a tendency towards improvement, with more than half of the parents seeing improvements in at least one cognitive domain, and one third see declines in at least one cognitive domain (Hoppe et al., 2019). Compared to formal neuropsychological testing, parents describe declines most often in executive and language functions, whereas verbal and figural memory performances seem to be the most impacted in neuropsychological testing. This gap between scientific and everyday psychological concepts can be explained by significant differences in demands between daily life tasks and psychometric task demands. Both types of measures are significant to the diagnostic process and to counseling (Hoppe et al., 2019).

Van Schoonefeld & Braun (2013) as well as Ramantani & Reuner (2018) reviewed the literature to establish a list of the most determining factors predicting neurodevelopmental outcome, including cognitive outcome, in paediatric epilepsy surgery patients. Various predictors of postsurgical neurodevelopmental outcome have been identified: First, at birth the epileptogenic pathology can occur or already be present and determine the further development.

The age at the start of epilepsy is an important predictor. During the course of epilepsy, its duration, the total number of seizures, the presence of epileptic spasms, the ASM use and load, the findings in the contralateral MRI as well as the presurgical IQ will greatly influence the postsurgical cognitive outcome. At time of surgery, the age at surgery, the side and the type of surgery as well as the completeness of resection of the lesion will impact the outcome. After surgery, the use of ASM, the drug load, the seizure status as well as the timing of cognitive assessment will influence the cognitive outcome measures.

In the following chapters of this dissertation at hand, an overview of the current state of knowledge about the most relevant pre-surgical, surgical, and post-surgical variables associated with cognitive outcome after paediatric epilepsy surgery will be presented.

1.5. Predictors of Cognitive Outcome after Epilepsy Surgery

1.5.1. Presurgical Cognitive Functioning

The association between preoperative cognitive performance and postsurgical cognitive outcome has been shown across many different neuropsychological functions and is a consistent observation in many studies (Skirrow et al., 2015; Kaur et al., 2022, Helmstaedter et al., 2020). Better preoperative performance bears the risk for greater postsurgical decline versus chances for improvement in poorer preoperative performance. However, even though the risk for loss after surgery is greater in good presurgical cognitive performance, higher presurgical functioning is still predictive of better overall postsurgical cognitive outcome (Helmstaedter et al., 2020; Puka et al., 2017).

1.5.1.1. Presurgical Intellectual Functioning. Paediatric epilepsy surgery candidates present with significantly lower intellectual functioning and higher rates of behavioral problems than healthy peers (Ramantani & Reuner, 2018; D'Argenzio et al., 2017). Higher presurgical IQ is associated with shorter epilepsy duration and with older age at seizure onset (Faramand et al., 2018). Presurgical IQ has been shown to be higher in children with neoplastic lesions, less presurgical trials of ASM, older age at seizure onset and shorter epilepsy duration as well as male gender (D'Argenzio et al., 2011; Faramand et al., 2018). Most research shows that post-operative cognitive level is well predicted by pre-operative cognitive performance, independently of other possibly influencing variables (Ramantani & Reuner, 2018; D'Argenzio et al., 2011; Smith & Baldeweg, 2017). For instance, in a cohort of epilepsy patients with resections of glioneuronal tumors, presurgical functioning strongly predicted the postsurgical

cognitive outcome and the epilepsy duration was related to the presurgical cognitive level (Ramantani et al., 2014).

1.5.1.2. Presurgical Circumscribed Cognitive Functions. Regarding circumscribed cognitive functions, children with good pre-operative memory performance are at higher risk for postsurgical verbal memory decline (Martin et al., 2016; Helmstaedter & Elger, 1998; Smith & Baldeweg, 2016). The authors argue that higher presurgical scores on neuropsychological tests are a marker for structural integrity, which means there is more functional capacity that resective surgery can put at risk (Martin et al., 2016). Especially temporo-mesial memory functions like long-term retrieval and consolidation depend on the presurgical level and the integrity of the contralateral mesial structures (Helmstaedter & Elger, 1998).

1.5.2. Etiology of Epilepsy

Etiologies involved in this study at hand are focal cortical dysplasias (FCD) and other malformations of cortical development (MCD), benign tumors, vascular caused lesions and perinatal hypoxic-ischemic events, post-traumatic epilepsies and mesial temporal lobe epilepsies.

1.5.2.1. Focal cortical dysplasia (FCD). These are localized malformative brain lesions, ranging from mild cortical dysplasia with difficult to visualize lesions (ILAE consensus classification system: Type I FCD) to well recognizable lesions on MRI of FCD Type II, and malformations associated with another principal lesion (FCD Type III) such as a hippocampal sclerosis, a tumor, a vascular malformation, or an abnormality adjacent to a lesion acquired during early life. Other forms of cortical developmental malformation are heterotopia and polymicrogyria.

1.5.2.2. Heterotopias. These are defined as clusters of well-formed neurons located in abnormal places, due to migration failures during brain development. These pathologies also lead to drug-resistant seizures (Barba et al., 2016). Surgery is often preceded by extensive presurgical evaluations including invasive Stereo-EEG, because the seizure onset-zone is often difficult to define, the seizure outcome is variable.

1.5.2.3. Polymicrogyria. Like heterotopia, polymicrogyria (PMG) is also due to abnormal migration of neurons in the cortex (Barba et al., 2016). During brain development these form an excessive number of very small gyri separated by shallow sulci. Functional MRI studies reveal that eloquent areas for language and motor function affected by PMG tend to carry functionality in the expected sites (Araujo et al., 2006). Hence surgical treatment is

provided to a limited number of patients who undergo extensive invasive recordings prior to surgery.

1.5.2.4. Low grade, benign tumors. These tumors (WHO grades I and II) are the second most frequent pathology leading to paediatric epilepsy surgery after FCDs (Holthausen et al., 2016). Gangliogliomas are the most frequent tumor type in this population, followed by DNET (dysembryoplastic neuro-epithelial tumors) and pilocystic astrocytomas. The risk for malignant transformation is usually very low in those tumors, but they are frequently associated with epilepsy, which is why they are referred to as LEATs in the research literature (Long-term Epilepsy-Associated-Tumor(s), Luyken et al., 2003). The treatment of choice is epilepsy surgery with a good perspective of long-term seizure freedom in about 70-88% (Chavez Lopez et al., 2022; Vogt et al., 2018; Mann et al., 2022; Ko et al., 2019). Drug resistance does not need to be proved before the surgical intervention and cooperation with specialized oncologists is recommended.

1.5.2.5. Vascular causes and perinatal hypoxic-ischemic events. They represent 6-11% of etiologies in paediatric epilepsy surgery cohorts (Harvey et al., 2008). Pre- and perinatal lesions comprise the following in decreasing frequency: arterial ischemic strokes and associated porencephalic cysts, venous stroke and cerebral sinovenous thrombosis, intracranial hemorrhage and hemorrhagic stroke in term infants, watershed lesions and ulegyria due to hypoxic ischemic events and vascular lesions in preterm children. Cerebral cavernous malformations, also known as cavernomas, which are vascular malformations, may also lead to paediatric epilepsy surgery (Metsähonkala et al., in Arzimanoglou et al., 2016). They can be solitary or multiple (Paddock et al., 2021).

1.5.2.6. Gliosis and glial scars. They are usually a result of central nervous system injury due to trauma, ischemia, following cerebral infections and stroke. Focal gliosis is epileptogenic brain tissue and is often an indication for epilepsy surgery (Dash et al., 2019).

1.5.2.7. Mesial temporal lobe epilepsy (MTLE). MTLE is a very frequent etiology in adult epilepsy surgery; however, it is rarer in children. Hippocampal sclerosis (HS), generally induced by complex febrile seizures or status epilepticus, is less common as a cause for intractable seizures in this age group. Tumors and FCDs are more frequent and HS appears more often as part of a dual pathology (Krsek et al., 2016). As dual pathology, FCD Type IIIa, which is abnormal cortical lamination adjacent to the HS or in the temporal lobe, is frequently observed in patients with MTLE (Blümcke et al., 2011).

1.5.2.8. Neuropsychological outcome of different etiologies. Only a few studies looked specifically at patients undergoing epilepsy surgery for FCD (Choi & Kim, 2019). In

FCD studies, patients with a younger age at epilepsy onset show more neuropsychological, often global cognitive deficits as well as patients with "catastrophic" epilepsy with daily seizures or repeated status epilepticus causing epileptic encephalopathy (Bast et al., 2006). Up to 50% of surgical patients with FCD are reported to have an IQ below 70 (Verseema et al., 2019; Kimura et al., 2019; Chen et al., 2014). The extent of the FCD lesion is reported to be related to the neuropsychological deficit of the child, especially the extent of blurring of the grey-white-matter junction is linked to impacted cognitive functioning (Lortie et al., 2022; Blackmon et al., 2015). 30% of paediatric patients show significant improvement in cognitive abilities after surgery, especially in the context of epileptic encephalopathy prior to surgery (Lortie et al., 2022; Verseema et al., 2019). Most surgical patients achieve a stabilization of their cognitive developmental course rather than marked improvement after surgery (Choi & Kim, 2019; Ramantani et al, 2013). Neuropsychological differences between the different FCD subgroups have rarely been investigated. Patients with FCD I seem the most impaired: In a cohort with 19 patients with postsurgically confirmed FCD I, all had severe cognitive impairment, no focal neurological symptom but one third had mild motor deficits (Holthausen et al., 2022). Maulisova and colleagues (2016) compared paediatric patients with temporal FCD type I and II with patients with dual pathology FCD and hippocampal sclerosis (FCD type IIIa). Except for visual short-term memory, where the dual pathology group had significantly lower scores, both groups did not differ in neuropsychological functions, including full scale IQ. Full scale IQ was 84, below average.

In patients with LEAT, the patients with pharmacoresistent epilepsy have a much higher risk for neurodevelopmental comorbidities than pharmacosensitive patients (Chavez Lopez et al., 2022). In children with LEAT, general IQ can range from intellectual deficiency to above average IQ, the mean being low average. Studies show that epilepsy surgery in patients with LEAT are usually safe in respect to cognitive functioning: In a recent study, paediatric patients who responded well to ASMs before surgery show an increase in verbal IQ after surgery, no other subcomponent of IQ showed significant pre- to postsurgical differences in the whole LEAT cohort (Chavez Lopez et al., 2022). LEAT are mostly located in the temporal lobe (Vogt et al., 2018; Chavez Lopez et al., 2022; Esteso Orduna et al., 2021). Vogt and colleagues showed, in a large cohort of 166 surgical patients with LEAT in the temporal lobe, that the cognitive outcome for these patients corresponds to what is commonly described for temporal lobe epilepsy and surgery (2022; more information in chapter 1.5.5.1). Memory was impaired prior to surgery in almost 2/3 of patients, EF in 45% and language also in 45%. Individual significant decline in memory was observed in 1/3 of patients. Risk factors for memory decline

after surgery are also the same as in other TLE, namely higher baseline performance, mesial location, left sided surgery and hippocampal resection (Vogt et al., 2018). Predictors for EF were ASM load and duration of epilepsy. EF stayed stable in 2/3 of patients after surgery and improved in 20%. DNET and gangliogliomas have better cognitive and seizure outcome, compared to pylocystic astrocytoma (Vogt et al., 2022). In another recent study by Mann and colleagues (2022), evaluating cognition in LEAT in a mixed cohort of children and adults, in which 27 out of 35 participants had a temporal tumor location, presurgical cognitive deficits were also very frequent with 65.7% of patients with relevant deficits in one or more cognitive domains. Learning and memory deficits were present in 60%, attentional dysfunction in 22.9%, EF dysfunction in 25.7%. After surgery, maximum improvement was measured at the 12-month follow-up, after which the cognitive functions stayed stable: relevant deficits were present in only 51.4% of patients and a significant improvement of nonverbal learning and memory capacities was observed. Other cognitive functions remained stable. Ko and colleagues (2019) found an association between younger age at seizure onset, longer epilepsy duration, more antiseizure drugs at time of surgery, multilobar tumor involvement, presence of generalized epileptic discharges and a lower presurgical Full Scale IQ (FSIQ) in children with LEAT. Furthermore, postoperative FSIQ was predicted by preoperative FSIQ.

In many paediatric studies, the epilepsy surgery cohort is composed of patients with differing etiologies and some propose comparisons of the different etiologies: In a cohort of patients who had extratemporal epilepsy surgery, the brain tumor group had a higher presurgical global IQ than the FCD group (D'Argenzio et al., 2011). Studies on paediatric frontal lobe surgeries showed a lower risk for postsurgical cognitive losses in patients with benign tumors, compared to patients with FCD (Ramantani et al., 2018b, Chieffo et al., 2011).

Presurgically, children with a dual pathology of FCD and HS have greater cognitive deficiencies than children with single pathologies like HS, FCD or tumor in the temporal lobe. As shown in other studies, tumor patients show the best performance (Bigel & Smith, 2001).

Only case studies focus on cognition in patients with vascular malformations, such as cerebral cavernous malformations and AVM exist currently. Paediatric cases are rare, possibly since 95% of cases become symptomatic during the second and third decade of life (Chavez et al., 2016) and scientific literature focuses on surgical procedures and seizure outcome. In a case report of 3 adolescents with focal frontal vascular malformation, specific cognitive functions were disturbed prior to surgery but differently in every patient and significant improvements in EF were observed after surgery in all three cases (Chavez et al., 2016).

In children with perinatal stroke, cognitive impairment is a risk factor for the appearance of epilepsy (Rattani et al., 2019; Elgendy et al., 2022). Almost 30% develop epilepsy and 1/3 of these children develop mild language impairment, especially difficulties with complex syntax and morphological errors, mostly due to reorganization of language networks in the brain after the stroke. After extensive left hemispheric stroke damage, there is a 60% chance of right hemisphere language dominance, whereas the chance is only 15% in patients with left hemispheric malformation or tumor (Lidzba et al., 2021). Elgendy and colleagues report one fifth of the toddlers to have mild or severe developmental delay after perinatal stroke (2022). These patients also have an increased risk for Developmental/Epileptic Encephalopathy with Spike Wave Activation in Sleep (DEE-SWAS), formerly known as CSWS (Rattani et al,. 2019), which is known to alter language development, to cause important attention difficulties, abnormal impulsive and inappropriate behavior, and ultimately a global developmental delay (Specchio et al., 2022). This delay can partly be reversible if the epileptic activation during sleep can be interrupted through therapy. Studies about epilepsy surgery in this patient group focuses on hemispherectomy, on stereo-EEG and seizure outcome studies, no studies specifically on postsurgical cognitive development could be found.

Gliosis usually appears after perinatal stroke, hypoglycaemia and perinatal asphyxia as well as after encephalitis. In most studies, gliosis is not specifically examined but added to the subgroups of the underlying etiology. In a rare study on epilepsy in children with parieto-occipital gliosis, epileptic encephalopathy based on clinical-electrophysiological findings was seen in almost 40% of patients, almost 72% had a global developmental delay and 36% had a visual impairment (Ray et al., 2021).

Neuropsychology of mesial temporal lobe epilepsy is treated in detail in chapter 1.5.5. Localization of Epilepsy, therefore it will not be discussed here in order to avoid redundance.

1.5.3. Surgery type

The surgical techniques investigated in this study at hand are lesionectomy, intralobar tailored resection, multilobar tailored resection, selective mesial-temporal resection called amygdalohippocampectomy (AHE), standard anterior temporal resection with or without AHE, and temporal tailored resections. Lesionectomy is the most frequent surgical technique in paediatric epilepsy surgery and is defined as a limited, focal resection of an epileptogenic brain lesion visible on MRI (Blauwblomme et al., 2016). In tailored resections, for instance in the temporal tailored resection, which is a tailored cortico-amygdalohippocampectomy approach,

the extent of resection is dictated by the patient´s preoperative and intraoperative findings (Falowski et al., 2012).

Very few studies in paediatric epilepsy surgery focus on cognitive outcome of different surgical methods in epilepsy surgery, except for hemispherectomies. This may be due to less homogenic groups in paediatric cohorts than in older patients: mixed pathologies are frequent, differing surgical approaches and small sample sizes make it difficult to obtain publishable study results (Beaton et al., 2012). In a review of epilepsy surgery literature with strict inclusion criteria, Sherman and colleagues did not find a large effect of surgical technique on cognitive outcome in studies with predominantly adult patients, the number of paediatric studies were to low to draw conclusions (Sherman et al., 2011). Beaton and colleagues published a case series (2012) about 10 pediatic patients with unilateral hippocampal sclerosis who had transsylvian selective amygdalohippocampectomy with very encouraging results. They found 87.5% seizure free patients 2 years after surgery, as well as no significant gain or decline at a group level in intelligence as well as in visual and verbal memory. Improvements or maintenance of performance were noted in all patients in verbal and perceptual reasoning. On group level, an increase in immediate and delayed recall of faces was observed. In a cohort of 89 paediatric patients undergoing surgical treatment for temporal lobe epilepsy, different surgical methods were compared, evaluating seizure control afterwards as well as neuropsychological testing (Clusmann et al., 2003). Leftsided amygdalohippocampectomies showed lower rates of seizure freedom after surgery than anterior temporal lobectomies (74-77% vs 94%). On an individual level, some patients had verbal memory deterioration after left-sided operations, neuropsychological deteriorations were very rare after right temporal lobe surgery. Attention and contralateral functions were mostly improved after surgical intervention. Law et al. (2017) also observed verbal memory decline in patients with left language representation undergoing left temporal lobe surgery that included mesial structures, whereas children with left TLE surgery and spared mesial structures showed no postsurgical change in memory performance. Children with right TLE also showed no postsurgical change in memory performance.

Multilobar resections correspond to one-fifth of paediatric epilepsy surgery and lead to seizure freedom in only 48% of patients in a study by Kogias and colleagues (2020). Most important predictor of seizure freedom is the epileptic zone being distant from eloquent areas, which implies a greater chance of complete resection of the epileptogenic zone. In a group of paediatric and adult patients undergoing multilobar disconnective epilepsy surgery in the posterior quadrant, almost 30% of patients had impairments of different cognitive domains before surgery, including Flexibility and Working Memory. After surgery verbal and visual

Working Memory improved, Flexibility performance did not (Rizzi et al., 2019). In another multilobar disconnective epilepsy surgery cohort of 11 children, 45% had an intellectual disability. After surgery, 9 out of 11 children showed a stable cognitive development or improved independently of seizure status (Limpo et al., 2023). More studies on neuropsychological outcomes after multilobar interventions in children are needed (Jones et al., 2022).

1.5.4. Side of Surgery

In a study with children undergoing epilepsy surgery for glioneuronal tumors, the presurgical neuropsychological evaluation showed significantly lower performances of patients with left hemispheric tumors in verbal IQ, in verbal learning and delayed recall as well as in reading than patients with right hemispheric lesions (Garcia-Fernandez et al., 2011). After surgery, neuropsychological outcomes were stable or improved.

Children with temporal lesions with atypical language representation, with eloquent language areas on the right hemisphere, have lower abstract reasoning capacities and verbal Working Memory as well as receptive vocabulary than those with typical language representation (Maulisova et al., 2016).

Other significant differences in memory and in language functions after left or right sided surgeries have been described and are reported in further detail in the next chapter 1.5.5. Localization of Epilepsy Surgery. Most studies are focused on the comparison of cognition in right vs left temporal surgeries, because eloquent areas for memory and language functions are localized there.

1.5.5. Localization of Epilepsy Surgery

Most paediatric epilepsy surgery studies up to date have examined the effects of resections to the temporal lobe, followed by frontal lobe surgeries. Relatively little research has been done on effects of occipital and parietal lobe surgery (Smith & Baldeweg, 2017). This is not surprising, since surgery of the temporal lobe is the most frequent focal resection in paediatric epilepsy surgery with 23.2 %, followed by frontal resections (17.2%); parietal (2.8%) and occipital surgeries (1.7%) are much rarer (Harvey et al., 2008). Multilobar interventions cover 12.9% of paediatric epilepsy surgeries.

A comprehensive overview of neuropsychological outcomes after epilepsy surgery in different localizations is given in the following. It is not exhaustive, because this would extend far beyond the scope of this dissertation.

1.5.5.1. Temporal Lobe Surgeries. As mentioned before, results regarding ***memory performance*** in children with temporal lobe surgeries are contradicting and therefore one should be careful in trying to localize memory functions in children: Children undergoing surgery in the left temporal lobe showed significantly poorer verbal memory performance than predicted, based on their pre-surgical performance in a paediatric cohort of epilepsy surgeries 6 and 12 months after surgery (Meekes et al., 2013). In comparison, verbal memory performance was consistent with pre-surgical baseline in most of the children with extratemporal or right temporal resections. One year after surgery, Jambaqué et al. (2007), found a material-specific memory effect in children: children with left temporal lobe epilepsy (TLE) had worse verbal memory results whereas children with right TLE had worse visual memory results. Law et al. (2017) assessed change in verbal memory performance one year after surgery. They divided children into one group with TL surgery sparing the mesial structures and one group with temporal lobectomy including the resection of mesial structures. Children who underwent left temporal lobe surgery that included mesial structures showed a verbal memory decline, especially when language representation was in the left hemisphere and when preoperative verbal memory was intact. Children with left language representation and spared mesial structures showed no change in verbal memory from preoperative to follow-up assessment. Seizure status did not show any impact on verbal memory performances after surgery. Helmstaedter and Elger (1998) showed in a large group of children and adults undergoing left anterior temporal lobectomy, including mesial and cortical temporal structures, that verbal learning capacities were depending on preoperative performance as well as on age: the older the patient at surgery, the greater was the postoperative impairment. Children up to age 15, which is the estimated age limit for cerebral plasticity, demonstrated improvement after surgery. Whereas the 15-30 years old, supposedly the time in which behavioral compensation is strongest, showed a significant decline in postsurgical verbal learning capacities. The patients above age 30, when behavioral compensation abilities start to decline, showed the most significant deterioration. Verbal learning also depended on language ability, with better language function leading to less decline. The authors hypothesize that since verbal learning depends strongly on short-term and Working Memory, it can in part be compensated for, by other left hemispheric functions like language. Changes in consolidation and retrieval of information in memory did not depend on age or language function but only on preoperative performance, reflecting the temporomesial dysfunction of LTLE, with performance depending on the integrity and functional recruitment of right mesial structures.

In a comparative study, Gleissner et al. (2005) showed a significant decline in left-temporal resected adults and children in verbal learning, as well as a decline in visual memory in right-resected patients 3 months after surgery. However, the children recovered and attained preoperative levels in verbal and visual learning 9 months after surgery, whereas adults remained significantly worse than their preoperative level. The authors suggested higher compensational capacities and greater plasticity accounting for the better outcome in paediatric patients.

In comparison with adults, children seem less vulnerable to memory decline following TL surgery. However, adults and children with TLE may constitute a different entity, because of diverging etiologies: adults mostly have surgery for mesial sclerosis whereas children have more often benign tumors, cortical dysplasia or double diagnoses (Gleissner et al., 2005). In the study by Gleissner (2005) the author controlled for etiology, however this is not done in most studies about TL surgery in paediatrics.

In a long-term follow-up study (range 5-15 years post-surgery) with paediatric patients undergoing unilateral temporal lobes resections, Skirrow and colleagues (2015) found no significant difference between left and right TLE patients at presurgical baseline as well as no pre- to postoperative deteriorations in memory performance. In contrast, increased performance in verbal episodic memory was found after right temporal lobe surgery and visual episodic memory improved after left temporal lobe surgery. The authors suggested functional release of memory function in the unoperated temporal lobe after seizure reduction or cessation. In addition, the authors found better verbal episodic memory at follow-up in left TLE patients with greater hippocampal sparing during surgery, as well as better semantic memory in left TLE patients with greater temporal pole integrity and smaller resection volume in the temporal lobe. Similar results were found in another long-term follow-up study (range 4-11 years post-surgery) by Puka & Smith (2016): They also found no significant differences between left and right TL surgery patients at baseline, at long-term follow-up patients with right temporal lobe epilepsy had significantly higher scores in story recall. In a longitudinal study, Gonzalez et al. (2012) showed that memory in left TLE paediatric patients tended to remain stable whereas it improved in right TLE, independent of seizure status, mood or IQ.

The primary cause of lack of conclusive evidence on postsurgical cognitive outcomes in the paediatric population could be due to flaws in methodology and in small, heterogeneous sample sizes and mostly short follow up periods, improvements may be seen in subgroups of children in regard to laterality or site (Sibilia et al., 2017, Ramantani & Reuner 2018).

In studies evaluating ***language development*** in paediatric patients with TLE surgery, results are also inconclusive: Blanchette & Smith (2002) compared children who were undergoing temporal or frontal lobe epilepsy surgery, in their language capacity (expressive and receptive vocabulary, comprehension, reading, spelling, phonemic Fluency and category Fluency). Results showed no effect of localization of surgery on language function. However, before surgery, children with left hemisphere lesions had lower scores on comprehension and category Fluency. Other measures did not differ between children with left or right hemisphere lesions and no postsurgical change in language capacities was observed. No postsurgical change in naming and word Fluency 3 and 12 months after surgery was also noted after temporal lobe resection in paediatric patients, except for children with a postsurgial increase in verbal learning capacity in a study by Gleissner and colleagues (2005). On the other hand, one year after surgery, Vega and colleagues (2015) found declined naming performances after left, but not right, paediatric temporal lobe resections, in accordance with postsurgical results found in adults with TLE. No change was observed in verbal Fluency. Furthermore, in a study comparing children, who had anterior temporal lobectomy for TLE, to normative data, 2 years after surgery language development slowed down, causing increased language delay in productive lexicon, receptive lexicon and productive syntax, only receptive syntax developed at a normal pace. Slowing of development of productive lexicon was particularly slow in children with left language dominance and surgery on the left hemisphere (de Koning et al., 2009).

Regarding ***other neuropsychological functions*** in children with TLE, improved attention, Working Memory scores and naming performances have been described one year after epilepsy surgery (Jambaqué et al., 2008). Improved attention and short-term memory, as well as a tendency for improvement in manual motor coordination was also found in TLE and FLE patients one year after surgery in a study by Lendt and colleagues (2002). Gleissner et al. (2005) found improved attentional capacities one year after temporal lobe resections in children, independent of side of surgery. Right-resected children experienced a significant loss in visuospatial functions 3 months after surgery, but most children had regained their presurgical level one year after surgery. Chieffo and colleagues found deficits in naming, visual memory and visuo-spatial attention prior to surgery in TLE patients with a stable outcome after surgery, whereas FLE patients showed more EF deficits and motor impairment and more often individual deterioration after surgery (2011). Compared to healthy controls and children with FLE, TLE patients present more often with impaired emotional control and with verbal Working Memory impairment. Compared to healthy peers, they also presented with deficits of EF, but less than patients with FLE (Esteso Orduna et al., 2021).

In a study comparing children with temporal lobe epilepsy surgery for different neuropathologies, the dual pathology group had lower intelligence scores, as well as lower scores on delayed visual memory, in executive functioning, in expressive language abilities and in academic tests than the tumor group and the hippocampal sclerosis group (Bigel et al., 2001).

1.5.5.2. Frontal Lobe Surgery. In children undergoing frontal lobe surgery, presurgical IQ in a surgical group was below average in half of the cohort, in accordance with another study on extratemporal paediatric epilepsy surgery (Chieffo et al., 2011; D'Argenzio et al., 2011). Deficits in verbal memory, in visuomotor integration and in executive functions, especially in verbal word Fluency, before surgery have been described in FLE patients (Chieffo et al., 2011). Authors hypothesize memory problems in paediatric FLE are due to difficulties in strategic organization of material rather than encoding problems as in TLE (Chieffo et al., 2011; Esteso Orduna et al., 2021). Further in paediatric FLE, postsurgical IQ revealed no significant change on a group level (Ramantani et al., 2018b). 12% of patients with frontal lobe surgery showed significant improvements in overall cognition, 16% experienced deterioration - all with FCD (Ramantani et al., 2018b). Similar results were presented in another study on children with frontal lobe surgery: In presurgical assessment, children with surgery for TLE showed the same IQ on group level than those with surgery for FLE (Chieffo et al., 2011). The FLE group showed more frequently difficulties in motor coordination and in executive functions before surgery, and 2 years after surgery slight deterioration in IQ and executive functions was observed despite behavioral improvement. 91% of their FLE patients became seizure free. Lendt and colleagues (2002) also found more persurgical manual motor coordination difficulties in FLE patients than in TLE patients. However, IQ was in the normative range and significantly higher in their FLE group than the TLE group before surgery. One year after surgery, they noted no postsurgical change in IQ and EF functions in both groups. However, only 58% of their FLE patients had Engel I outcome, maybe accounting for a more conservative surgical approach, sparing more functional brain tissue. Furthermore Lendt´s cohort was 6 years older at surgery, so longer epilepsy duration could have contributed to the more pronounced deficits, In a study comparing children with TLE, FLE and healthy peers, both epilepsy groups had impairments of EF, but the FLE group showed the lowest scores, especially Flexibility was impacted (Esteso Orduna et al., 2021).

1.5.5.3. Posterior Cortex Surgery. Due to intrinsic difficulties in delineating the boundaries between the posterior edge of the temporal lobe, the occipital and parietal lobes, epilepsies emerging from these areas can be grouped together into posterior cortex epilepsies (PCE; Sierra-Marcos et al., 2017). Moreover, epilepsy surgeries in posterior regions sum up to

less than 5% of paediatric epilepsy surgeries, so combining the occipital and parietal resections allow to create cohorts large enough for research investigations (Harvey et al., 2008). In fact, rapid propagation of epileptic activity and frequent involvement of eloquent areas, i.e. for language and vision, exclude a lot of patients with PCE from surgery (Sierra-Marco et al., 2017). Children with PCE have a low mean IQ of 74, those with well-defined lesions (tumors, FCD-II) had higher IQs. Variables predicting postsurgical improvement were a well-defined lesion and a decrease in number of AEDs.

1.5.5.4. Parietal Lobe Surgery. Surgery for parietal lobe epilepsy (PLE) is rather rare, because PLE only accounts for less than 5% of partial epilepsies, therefore only few studies with small patient cohorts exist. As presented above, most studies have mixed cohorts of posterior epilepsies, including occipital lobe epilepsies (OLE) (Gleissner et al., 2008). The most frequent cause for PLE is tumors. Gleissner and colleagues (2008) evaluated children with surgically treated parietal lobe epilepsy (PLE). Seizure outcome in the one year follow-up was very good with 87% seizure free patients. Presurgical IQ was in the subaverage range, 29% scored in the range of intellectual disability (IQ below 70), and IQ did not change significantly after surgery. Age of onset of epilepsy did not correlate with presurgical IQ. Left and right PLE patients did not differ significantly in the presurgical evaluation, but functional deficits discordant with the lesion side was frequently observed (i.e. visuospatial difficulties in left and language problems in right PLE). Postoperative improvement of attentional functions was frequent. No neurological deficit was observed after surgery, differing from adults after PLE surgery, in which a temporary partial hemisensory or Gerstmann Syndrome had been observed in 27% of patients (Binder et al., 2009).

1.5.5.5. Multilobar Resections. Children undergoing multilobar resections more often exhibit global cognitive impairment before surgery than children undergoing focal lesionectomy (Freitag & Tuxhorn, 2005). Smith and colleagues (2004) found that the lesion extent (unilobar vs. multilobar) predicted the change in the Perceptual Organization Index with decreasing score over time in the multilobar group, but not in the single-lobe group.

1.5.6. Age at Onset

In general, younger age at epilepsy onset has been associated with lower IQ, often intellectual disability, in paediatric surgery candidates (Bast et al., 2006). This has been observed in numerous studies, as for instance in these following examples: Lower IQ has been observed in the presence of daily seizures before the age of two and regardless of etiology (Sibilia et al., 2017; Vasconcellos et al., 2001). Two years after the first neuropsychological

assessment, developmental trajectory only improved in children who underwent surgery (Sibilia et al., 2017). When the age at onset was younger, a lower pre-surgical IQ in patients undergoing frontal lobe epilepsy surgery could be observed (Ramantani et al., 2018b). Jambaqué et al. (2007) also showed a lower performance IQ, as well as lower capacities in visuo-construction and in naming after surgery in children with an earlier age at onset of epilepsy. In a surgical group of children with glioneuronal tumors, patients with an epilepsy onset before the age of 6 had worse performances in multiple domains, including IQ, motor rapidity and hand coordination, visuo-constructional praxis, verbal reasoning, visual memory, concept formation and arithmetic at presurgical assessment (Garcia-Fernandez et al., 2011). After surgery no variations in neuropsychological performance was seen in the early onset group, whereas small improvements were seen in the late onset group in visual attention, in word and nonverbal Fluency, in verbal learning and verbal delayed recall. In another study with LEAT, a young age at seizure onset was also associated with more pronounced cognitive deficits (Mann et al., 2022).

1.5.7. Duration of Epilepsy Prior to Surgery

Appropriate timing of surgical intervention is of utmost importance in paediatric epilepsy surgery, since it is one of the only potentially modifiable outcome predictors (Ramantani et al., 2018b). Shorter epilepsy duration is associated with higher cognitive scores and with a stabilized velocity of cognitive development after lobar resections and hemispheric dysconnections (Kadish et al., 2019). Several paediatric studies have supported this overall positive effect of early surgical intervention on cognition (Freitag & Tuxhorn, 2005, Gleissner et al., 2005; Chieffo et al., 2011: Englot et al., 2013). In glioneuronal tumor resections, shorter duration of epilepsy is linked to a favorable cognitive outcome on a group level, despite individual deteriorations (Ramantani et al., 2014). Vendrame and colleagues suggest that long-term epilepsy may reduce brain plasticity and therefore a long duration of epilepsy might hinder possible postoperative gains in cognitive function (2009). In the youth, not only duration of epilepsy plays an important role, as well as age at surgery: Adolescents memory capacity does not recover as well after surgery as it does in younger children, which speaks for lesser brain plasticity with rising age (Helmstaedter & Elger, 2009).

1.5.8. Seizure Outcome

Whether seizure control really affects positively the cognitive outcome, as it is usually assumed, hoped for and presented in various publications (i.e, Lo Russo et al., in Arzimanoglou et al., 2016), remains open for discussion as the study results are inconclusive: In a study by Freitag & Tuxhorn (2005) catch-up of development was possible in preschool aged children only if they were seizure-free. The cohort consisted of very young children aged 3 to 5 years treated by surgery for severe epilepsy of various etiologies and locations. In older children, in a study on long-term effects of seizure freedom on intellectual development, improvement was shown 4 to 11 years after the first neuropsychological assessment, whether seizure freedom was obtained through surgery or other means (Puka, Tavares & Smith, 2017). In another long-term outcome study (5-21 years) of patients who underwent epilepsy surgery as children, improvement of processing speed occurred parallel to seizure control (Hallböök et al., 2013). In a study by Martin and colleagues (2016) memory improvements after paediatric epilepsy surgery were observed only in the seizure free group, especially in patients with FLE. Kaur and colleagues (2022) also found reduced probability for increased verbal memory capacity as well as higher odds of decline on visuospatial skills one year after epilepsy surgery in a group with persistent seizures compared to seizure free patients.

Other authors did not find improvements in cognition through seizure freedom: Children (mean age 9.3 ∓ 8.8 years) who had undergone surgery for extratemporal epilepsy showed no influence of postsurgical seizure freedom on the cognitive outcome, which remained unchanged after surgery (D'Argenzio et al., 2011). Lendt and colleagues (2002) did also find no effect of seizure status on neuropsychological outcome in both FLE and TLE patients one year after surgery, neither did Smith and colleagues in a mixed surgical cohort (Smith et al., 2004).

1.5.9. ASM Load

ASM cessation was shown to be the strongest predictor of postoperative improvement in IQ in children after temporal lobe surgery (Skirrow et al., 2011). In a large multicenter study with 301 paediatric patients, this could be confirmed: The start of ASM withdrawal, the reduction of the number of ASMs and the complete ASM withdrawal were all associated with improved postsurgical IQ scores and even gains in IQ, independent of other determinants of cognitive outcome (Boshuisen et al., 2015). A study evaluating the impact of postoperative antiseizure medication (ASM) withdrawal on psychomotor speed in seizure-free paediatric patients, showed significant improvement in the withdrawal group compared to the no-

withdrawal group 24 months after surgery (Van Schooneveld et al., 2013). This was confirmed in a long-term follow-up study of patients who underwent epilepsy surgery 5-21 years prior as children: in seizure free patients, processing speed improved significantly and even more in subjects with no ASM (Hallböök et al., 2013).

An overview of paediatric epilepsy, epilepsy surgery, cognitive development and the most frequently described variables influencing cognitive outcome after paediatric epilepsy surgery has now been presented. One way to usually look at cognitive outcome is to choose a group which undergoes epilepsy surgery in the same localization and to look at cognitive changes occurring in this group. However, localization of cognitive functions in the immature brain is particularly challenging and mostly not suitable because of the ongoing development and enhanced plasticity in this age group (ref. preceding chapters). Another way to look at it, rather rare, is to look at how one cognitive function evolves after surgery, for a whole surgical cohort with different surgery localizations. EF dysfunction is very frequent across different types of epilepsy (i.e. Reuner et al., 2016; Helmstaedter et al., 2019) and so it is justified to look out for it in a whole epilepsy surgery cohort. Therefore, this will constitute the main focus of this dissertation at hand.

1.6. Aim and Research Questions

The aim of the present study was to investigate the longitudinal development of executive functions, following paediatric resective epilepsy surgery and to determine patient-, epilepsy- and epilepsy surgery related factors – called clinical factors- which are predictive of change over time. Since there is very limited literature on executive functioning after epilepsy surgery in the paediatric population, an explorative analysis of EF in this research work was prioritized. Hypotheses could only be derived from basic research on EF and from findings on cognitive functioning after epilepsy surgery. The following research questions were investigated:

(1) How do executive functions develop after paediatric epilepsy surgery over time, are there different developmental pathways for specific executive functions? Regarding the effect of time after surgery, no long-term studies on EF development after paediatric epilepsy surgery have been published that could lead to formulating hypotheses. However, studies on long-term IQ development showed improvements appearing 2 or more years after surgery and short-term studies of some features of EF in specific groups after paediatric epilepsy surgery showed improvements. Therefore, it could expect EF improvements appearing over time. The extant literature offers little basis to propose hypotheses with respect to effects, specific to the different features of executive functioning.

(2) How do the clinical factors presurgical IQ, side of surgery, etiology, type of surgery, localization of surgery, age at epilepsy onset, duration of epilepsy prior surgery, seizure outcome and ASM drug load, and time between surgery and the outcome evaluations influence the development of executive functions and can predictors be identified? It was hypothesized that presurgical IQ would highly influence postsurgical EF. The extant literature could not offer information to propose hypotheses regarding EF development regarding side of surgery or surgery type. It was hypothesized that development of EF would vary in regard of the etiology and expected patients with tumors to show the most significant improvement over time after surgery. It was hypothesized that the impact of localization of the resective surgery on EF would vary. Given the importance of the integrity of the frontal lobes for EF, patients who had undergone surgery on this lobe were expected to decline after surgery and to show no improvement over time. According to literature, patients with extrafrontal surgical locations were expected to improve after surgery. Patients with older age at epilepsy onset and shorter duration of epilepsy were expected to have a more favorable development of EF over time. It was assumed that seizure freedom would be linked to a better EF development after surgery. It was hypothesized that a higher ASM drug load would hinder postsurgical EF improvement over time.

(3) Which clinical factors are associated with significant EF decline or improvement after paediatric epilepsy surgery? Individual analyses of patients with significant changes after surgery should investigate this question and the same clinical factors were expected to influence the EF outcome as in the group analysis.

2. Material and Methods

2.1. Study Design

This is an observational and retrospective analysis of longitudinal data of a clinical cohort of children and adolescents who underwent epilepsy surgery. The study is multicentric, involving data from two German epilepsy centers: The Clinic for Children and Adolescents of the Epilepsy Center Kork and the Epilepsy Unit of the Children's Hospital, University Hospital of Heidelberg. The retrospective data collection comprises the psychometric results on EF tasks of a presurgical neuropsychological assessment, and 4 postsurgical assessments (6, 12, 24 and 60 months after surgery), so 5 assessment times. In this cohort study, data analyses are explorative. First, descriptive analyses of the cohort are given. Second, for each investigated EF, an analysis of the effect of the independent variable time on the dependent variable EF is

investigated using univariate multilevel models. Third, for each investigated clinical variable, subgroups are formed within the cohort. For each analysis, the independent variables are a clinical factor and time, the dependent variable is again EF, and used in multivariate multilevel models. These subgroup analyses are followed by individual analysis of significant change over time for the same set of clinical variables. Positive votes from the Ethics Committee of the Medical Faculty of the University of Heidelberg (Genehmigungsnummer S-299/2017) and of the University of Freiburg (Antrag-Nr. EK-Freiburg: 401/17) were obtained. Because of the retrospective nature of the study, based on the analysis of already collected clinical data, the parents' consent to the study was not needed.

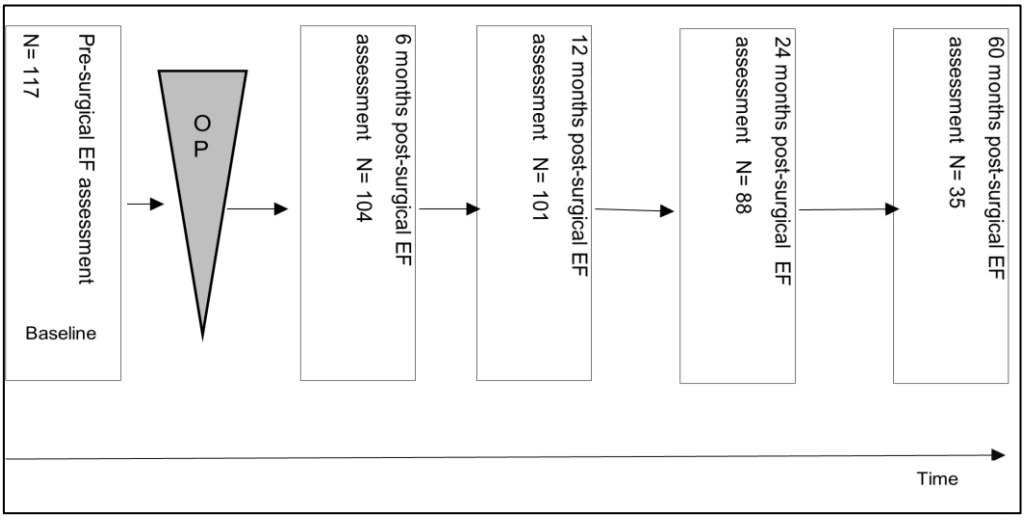

Figure 3: Schematic order of Executive Functions assessments.

Note. EF = Executive Functions; OP = surgery; N= number of patients

2.2. Sample

237 medical records of patients who underwent epilepsy surgery between 1998 and 2016 and who participated in neuropsychological assessment in one of the participating centers, were analyzed.

Included into this two-center study were children who had a preoperative IQ equal or above 70. They had to have undergone a presurgical neuropsychological assessment (baseline) as part of the presurgical candidacy evaluation as well as at least one postsurgical neuropsychological assessment. Neuropsychological data were extracted from patients' clinical records. Prior to surgery all patients had been unable to achieve seizure control from at least two trials of anti-seizure drugs (ASMs).

Exclusion criteria was an intellectual disability (IQ below 70), because these children usually present difficulties in executive functioning related to their disability. Also were excluded children with known genetic disorders such as SCN1 or phacomatoses, as well as neurogenerative disorders such as Rasmussen encephalitis, because it could not be ruled out, that executive difficulties result from the underlying condition. Excluded were children who underwent hemispherotomy or hemispherectomy, because they usually present extensive neurological impairment and the surgery's goal in general is not complete seizure control but palliative, i.e. to reduce drop attacks. Moreover, their often severe sensory-motor impairments place limitations on the type and amount of cognitive testing these children can undergo. Children aged under 4 years old at time of surgery were also excluded because of methodological difficulties to evaluate executive functioning at that age and therefore lack of assessment during neuropsychological presurgical workup.

2.3. Participant Demographics and Epilepsy Surgery Characteristics

117 children were selected for this study. 44 children were patients at the University Hospital Heidelberg, 73 patients were from the Epilepsy Center Kehl-Kork. Age range at time of surgery went from 4;6 to 18;10 years old, mean age at time of surgery was 12;10 years (*SD*= 3;10). At baseline, all these children received, as part of the presurgical candidacy evaluation a neuropsychological assessment. 104 of these children were reassessed at 6-months-post-surgery follow-up, 101 children at 12-months, 88 at 2-year and 35 at 5-year follow-up. There were 54% male (*N*=63) at baseline. Mean age at onset of epilepsy was 6;8 years (*SD*= 4;6). 33 patients (28%) underwent invasive presurgical EEG to determine the seizure onset. 64 patients (55%) had surgery on the right hemisphere. Surgery on the frontal lobe was performed in 35 cases (30%), on the temporal lobe in 50 (43%) and in posterior lobes in 10 (9%). Etiologies were confirmed by postsurgical histopathologic examination. Etiologies were mostly malformations of the cortical development (MCD) with 47 cases (40%), followed by tumors (*N*=31, 27%) and dual pathologies (*N*=23, 20%). There were 8 cases of gliosis (7%), 2 cases of vascular malformation (2%) and one case of lesion after vasculitis (1%). Most surgery types performed were intralobar tailored resections (*N*=37, 32%), followed by lesionectomies (*N*=28, 24%) and multilobar tailored resections (*N*=21, 18%). For a complete overview of participants demographics, as well as epilepsy surgery characteristics see in the Appendix 1.

2.4. Neuropsychological Assessment

The same routine presurgical neuropsychological test battery was used by the two participating centers (Appendix 2) with fixed intervals: shortly before surgery, and approximately 6, 12 and 24 months thereafter. At the Epilepsy Center Kork a 5- years- post-surgery assessment was also offered. For a variety of reasons (e.g. drop out, poor cooperation, age at baseline, time constraints), some patients had not completed the whole test battery and had not attended all the postsurgical evaluations. Therefore, data was not available for all patients on all tasks at all assessment times. All selected patients had been assessed at least twice, including a presurgical and one postsurgical assessment. In accordance with good clinical practice, tests and test versions were chosen according to the age of the children. Seizure outcome was measured using the Engel Classification system (Engel et al., 1993). Patient-, epilepsy- and surgery-related variables were obtained from patients' medical charts, including histopathology results and type and location of surgical resection.

As some patients had not completed the whole test battery and had not participated in all assessments offered post-surgically, numerous missing values were to be expected. Because of the heterogeneity of the tests used for each patient due to age, as well as the differences in reliability for the different tests, the initial idea of forming composite scores for distinct executive functions such as Flexibility or Inhibition had to be discarded. Instead, tests which were commonly used in research and presented in literature to measure executive functions, per patient were selected. The test selection comprised tests which were known to measure primarily planning, Problem Solving, Fluency, Working Memory, Inhibition, Monitoring, Flexibility. The selected tests were then analyzed longitudinally and in correlation with different clinical parameters. In order to allow statistical analysis of each test, at least 10 patient scores per test were needed for descriptive and explorative analysis and at least 35 patient scores were needed for explorative, univariate and multivariate multilevel modelling. The selected neuropsychological tests can be seen in Table 1. For some tests, different but comparable versions were used during assessments, i.e. digit span from the Wechsler test batteries and number recall from K-ABC. The results of these test versions were summed up to a composite score. The scores for which this procedure was applied can be seen in Table 2.

Table 1: Executive functions and corresponding neuropsychological tests

	Psychometric tests and cumulative measures assessing Executive Function	
Executive functions	**for univariate multilevel modelling**	**for multivariate multilevel modelling**
Planning	Block design[a]	Block design[a]
Problem Solving	Matrix reasoning[b]	Matrix reasoning[b]
Fluency	Phonological Fluency[a]	Phonological Fluency[a]
Working Memory	Digit span[a] Working Memory Index[b]	Digit span[a]
Inhibition	TAP GoNoGo time (Testbatterie zur Aufmerksamkeitsprüfung) TAP GoNoGo errors (Testbatterie zur Aufmerksamkeitsprüfung) D2-KL[a]	D2-KL[a]
Monitoring	TAP Divided attention errors (Testbatterie zur Aufmerksamkeitsprüfung)	/
Flexibility	Trail Making Test B Symbol search[b]	Symbol search[b]

Note. [a] cumulative measure, [b] from Wechsler test batteries , D2-KL: Konzentrationsleistung from the paper-pencil-test D2 (Brickenkamp et al., 2010), TAP: Testbatterie zur Aufmerksamkeitsprüfung (Zimmermann & Fimm, 1993).

Table 2: Cumulative measures from neuropsychological tests used as measures of Executive Functions

Cumulative measure	**Psychometric tests**
Digit span	Digit span (HAWIK-III, HAWIK-IV, WISC-V, HAWIE-R, WAIS-IV), Number recall (K-ABC I and II)
Block design	Block design (HAWIK-III, HAWIK-IV, WISC-V, HAWIE-R, WAIS-IV), Triangles (K-ABC I and II)
Phonological Fluency	COWA, RWT, PSB-R Untertest 5, VFT (D-KEFS)
Matrix reasoning	Matrix reasoning (HAWIK-III, HAWIK-IV, WISC-V, HAWIE-R, WAIS-IV), Pattern reasoning (Kaufmann-ABC I and II), Raven matrices (CPM, SPM)

Note. HAWIK-III, HAWIK-IV, WISC-V – different versions of the German adaptation of Wechsler Intelligence Scale for Children (Tewes et al., 1999; Petermann, 2010); HAWIE-R, WIE – different versions of the German adaption of Wechsler Intelligence Scale for Adults (Tewes, 1991; Petermann, 2012) ; K-ABC I and II – different versions of the German adaptation of Kaufmann Assessment Battery for Children (Melchers & Preuss, 1992; Kaufmann & Kaufmann, 2015); COWA, Controlled Oral Word Association (Tombaugh et al., 1999); RWT, Regensburger Wortflüssigkeitstest (Aschenbrenner, 2000); PSB-R, Prüfsystem für Schul- und Bildungsberatung (Abel, 1988); D-KEFS, VFT Delis-Kaplan executive functions system Verbal Fluency test (Delis et al., 2001); CPM, Coloured Progressive Matrices (Raven et al., 1996); SPM, Standard Progressive Matrices (Kratzmeier et al., 1988).

2.5. Material – Presentation of Executive Functions Measures

For measuring Planning, a cumulative measure `block design´ (Table 2) was used. The tasks consist in assembling coloured cubes or foam triangles to match pictures under a time constraint and evaluates the visual aspect of Planning through visuospatial construction abilities (Zappullo et al., 2021; Drechsler, 2018). For evaluating Problem Solving, a cumulative score `matrix reasoning´ (see Table 2) was assembled. Matrices are tasks which necessitate convergent thinking: a pattern must be chosen to logically complete a gap in a matrix or a set of patterns (Drechsler, 2018). The cumulative measure `phonological Fluency´ allowed to evaluate Fluency abilities (Drechsler, 2018; Aschenbrenner, 2000). In phonological Fluency tasks, the participant generates as many words following a phonemic criterion in limited time. Working Memory was evaluated using the composite score `digit span´. First, number sequences presented verbally need to be reproduced by the participant in order, second, in reverse order. These auditory verbal memory tasks have been used in many studies to evaluate Working Memory (Drechsler et al., 2018; Baddeley et al., 2021; Kadish et al., 2013). Working Memory was also evaluated using the Wechsler Working Memory index, a composite score extracted from the Wechsler Intelligence test batteries (Tewes et al., 1999; Petermann, 2010; Tewes, 1991; Petermann, 2012). Depending on the test battery version, the index is composed of a digit span task and another Working Memory task. Either it is a number-letter-sequence presented verbally, which the participant needs to separate into letters and numbers and put into ascending or alphabetical order. Or it is a visual Working Memory task called picture span, in which children view pictures in a stimulus book and select from options to indicate in order which pictures they saw. Inhibition was evaluated using the two measures ´reaction time´ and `errors´ extracted from the subtest Go No Go from the computer-based test battery TAP (Drechsler et al., 2018). It´s a choice-reaction task, in which participants are presented for a few milliseconds either a cross or a plus sign, and must give a button response for the cross, but not for the plus sign. For Monitoring, the errors committed in the computer-based task `divided attention´ from the TAP test battery were evaluated, as its score represents the performance Monitoring ability (Drechsler, 2018). In this test, simultaneous attention to visual and auditory stimuli sequences is necessary to give a button response when certain visual formations or 2 identical tones in a row appear. Inhibition was also investigated using the measure D2-KL from the paper-pencil cancellation test D2, in which the participant crosses out all letters “d” accompanied by two lines in rows of “d” and “p” with non, 1, 2, 3 or 4 lines as fast as possible. D2-KL corresponds to the number of correctly crossed out “d” minus the false positives, the

errors and was used as a measure for Inhibition (Lendt et al., 2001). The subtest symbol search from the Wechsler Intelligence test batteries (see Table 2) was used for evaluating Flexibility (Kadish et al., 2013). The trail making test was also administered as a test of Flexibility, as in other studies (Watanabe et al., 2005; Drechsler, 2018). It consists of two parts, A and B. In part A, participants need to connect 15 consecutively numbered circles in numerical order on one worksheet. In Part B, the participant is directed to connect 15 consecutively numbered and lettered circles on another worksheet, by alternating between numbers and letters in numerical and alphabetical order. As the representative score of this test, the measure of time for Part B was adopted.

2.6. Data Analysis

The statistical analyses were carried out using the software IBM SPSS version 25 (SPSS Inc., Chicago IL). To facilitate the statistical analysis, the neuropsychological test scores, which constitute the dependent variables, were transformed either into standardized z- scores (mean = 0, standard deviation =1), into scaled score points (mean = 10, standard deviation 3) or into standard scores (mean = 100, standard deviation = 15).

For all tests of significance an α- level of 5% (= .05) was determined. So, if the actual *p*-value was ≤ .05, the result of the test was considered statistically significant. Significance of correlations was evaluated according to Cohen (1988). Descriptive statistics were used for variables including medians and ranges for continuous variables and frequencies and percentages for categorical variables. Demographic and clinical factors were explored using chi-square analysis for categorical group comparisons and ANOVA for continuous group comparisons and Somers' D for measuring correlation of ordinal variables.

Exploratory analyses on the cognitive measures (EF) over the 5 neuropsychological evaluation times were performed using Multilevel Models (MLM). MLM with clinical factors and time as independent variables and selected neuropsychological test results as presented in Table 1 as dependent variables, were regarded as the best method in this study to identify predictors of change: Multilevel models allow the analysis of small sample sizes and correlated data, as in repetitive measures. Regarding missing values, as it is expected in retrospective data, MLM do not proceed to listwise deletion, but use the information of all available test results for the modeling. The clinical factors were either continuous or categorical variables, time was considered a categorical variable with the 5 evaluation times as features.

Univariate and multivariate MLM were created. The focus of the analysis laid on the fixed effects, the main effect of time and, in the multivariate models, on the other independent

variable (clinical factor), which influence the dependent variable. Also, the interaction effect of both variables was included in multivariate models. The interaction is regarded as most important as it examines the effect of the independent variable in dependence of time. Univariate analyses were used to model the effect of time on each EF in the whole cohort or when the sample size was too small to perform multivariate analysis. Nonindependence of observations due to repeated measures was modeled using compound symmetry, which assumes equal residual variances across all types of EF as well as covariances between and across these variables. This means that 2 parameters, one for the variance and one for the covariance were estimated and were determined to be equal over all testing times. In sum, there were 7 parameters to be estimated via the REML (Restricted Maximum Likelihood) Method: 1 parameter for the intercept, 4 parameters for the evaluation times and 2 parameters for the variance-covariance-structure of the residuals, which were treated as correlated. The assumption of approximately normal distributed residuals was checked via histograms and was fulfilled for all models.

Besides the evaluation of the main, fixed effects of all predictors, the F-Tests for the overall model are reported. The F-Tests for the overall models compare the estimated means of every feature of the variable and check for significance. Even when overall F-Tests or main effects were not significant, further analysis was conducted exploratively to check for differences between specific features of independent variables. Otherwise, these differences between features might not have been discovered: due to the large number of features, when i.e. only one feature out of 6 is significant, it can lead a main effect or an overall F-Test to be non-significant. This proceeding is recommended in explorative studies. Further analyses included: For categorical independent variables and time, estimated marginal means and standard errors were calculated to assess the differences between the categories, as well as between evaluation times. Further, pairwise comparisons between features helped to see how differences varied between testing times. Additionally, when the predictor had too many features, deviation contrasts were used instead or in addition of pairwise comparisons. Deviation contrasts compared every feature with the mean of all features. For continuous predictors, the regression coefficients (β) were assessed and reported as well as its significance. Because of the small sample sizes, statistical power was not expected to be high. Therefore, adjustment for multiple testing was not performed, in accordance with the retrospective and explorative nature of this study.

In order to answer the third research question, which is to identify the variables in which patients who improved, differed from those who declined significantly, the proportion

of patients who showed clinically meaningful change from baseline to follow-up was evaluated. To note significant changes between neuropsychological functioning before and after surgery, the evaluation 24 months after surgery was chosen, because a lot more data was available for this evaluation time, than for the 60 months postsurgical evaluation. Patients with clinically significant change were identified by change of at least one standard deviation between both evaluations, a criterion previously used in studies evaluating cognition after paediatric epilepsy surgery (Smith et al., 2006; Puka & Smith, 2016; Kaur et al., 2022). Potential differences between clinical subgroups (i.e. localization groups, surgery type groups) were analyzed using χ^2 or Fisher´s exact test fort categorical independent variables and the unpaired t-test, the Welch t-test or the Mann-Whitney-U-test for continuous independent variables, as appropriate. For the Fisher's exact test, the two-sided significance was interpreted.

Because of small sample sizes for the number of participants showing significant improvement or deterioration, no interactions between different independent variables could be analyzed. Some features of independent variables (IV) were modified to form larger subgroups to obtain interpretable results. The IV etiology was summed up: Previous analyses often showed significant differences between the tumor group and the rest of the cohort, so the two groups 'tumor' and 'others' were formed. The IV surgery type has also been cumulated: Previous analyses and studies often showed significant differences between larger and smaller, tailored resections. Large resections here included multilobar tailored resections as well as standard temporal resections with or without AHE and AHEs. Small resections were lesionectomies and intralobar tailored resections. For the IV localization, only two options were formed to be able to interpret the data despite very small sample sizes. Previous studies suggest the frontal lobe plays an important role in IQ and executive functions, which is why the dichotomy 'frontal' and 'extrafrontal' was chosen here.

Analyses of change could be conducted for all the variables used in the multilevel analyses, except for the variable Inhibition. Only one patient showed a significant change, an increase in performance 24 months after surgery.

The Medical Biometry and Computer Science team at the University Hospital in Heidelberg gave very valuable and important advice in statistical analysis, Dr. Anja Sanders and especially Jan Meis.

3. Results

3.1. Cohort Characteristics

3.1.1. Independent Variables Seizure Outcome and ASM Load

3.1.1.1. Postsurgical Outcome Regarding Seizure Status. The epilepsy outcome after surgery was evaluated with the Engel classification system (Wieser et al., 2001; Appendix 3). Six months after surgery 72% of the children were completely seizure free since surgery (Engel 1a), after five years 65% were still seizure free. Only 3% six months after surgery and 2% after five years reported no worthwhile improvement since surgery (Engel 4). Further details can be seen in Table 3.

Table 3: Number of patients (percentage of patients) per Engel seizure outcome class for every evaluation time

		Time			
		6 mo	12 mo	24 mo	60 mo
Seizure outcome class	1a	76 (72%)	70 (69%)	57 (62%)	28 (65%)
	1b	10 (10%)	13(13%)	14 (15%)	6 (14%)
	1c	2 (2%)	1 (1%)	1 (1%)	3 (7%)
	1d	2 (2%)	2 (2%)	6 (7%)	1 (2%)
	2a	4 (4%)	3 (3%)	6 (7%)	2 (5%)
	2b	2 (2%)	4 (4%)	1 (1%)	1 (2%)
	2c	0	0	0	0
	2d	0	0	0	0
	3a	6 (6%)	4 (4%)	6 (7%)	1 (2%)
	3b	0	0	0	0
	3c	0	0	0	0
	3d	0	0	0	0
	4a	1 (1%)	3 (3%)	1 (1%)	1 (2%)
	4b	2 (2%)	2 (2%)	0	0
	Total	105	102	92	43

3.1.1.2. Use of Antiseizure Medications (ASM) Before and After Surgery. Prior to surgery, at the time of neuropsychological assessment, only 2% (n=2) of the patients did not take any ASM. Most patients took one, two or three different ASMs (27% - n=32, 51% - n=60 and 17% - n=20 respectively). At the 6 months post-surgical assessment, approximately half of the patients (53% - n=62) took only one ASM, only 3% (n=3) took three ASM. Only 1% (n=1) had completely discontinued ASMs. Five years after surgery, 24% (n=11) had been able to stop

taking ASMs. Most patients still took one or two ASMs (46% - n=21 and 30% - n=14). Additional details are reported in Table 4.

Table 4: Number of patients (percent of patients) at each evaluation time taking 0, 1, 2, 3 or 4 antiseizure medications.

		Time				
		Pre.	6 mo	12 mo	24 mo	60 mo
Number of ASM	0	2 (2%)	1 (1%)	7 (6%)	26 (25%)	11 (24%)
	1	32 (27%)	62 (53%)	63 (56%)	48 (46%)	21 (46%)
	2	60 (51%)	50 (43%)	35 (31%)	28 (27%)	14 (30%)
	3	20 (17%)	3 (3%)	6 (5%)	3 (3%)	0
	4	3 (3%)	0	1 (1%)	0	0
	Total	117	116	112	105	46

Note. Pre = presurgical evaluation, 6 mo= 6 months post-surgical evaluation, 12 mo= 12 months post-surgical evaluation, 24 mo = 24 months post- surgical evaluation, 60 mo = 60 months post-surgical evaluation, ASM = Anti-seizure medication, Total = total number of patients at each evaluation time.

Correlation between Engel class seizure outcome and ASM load after surgery: Somers' D showed that the use of different ASMs after surgery is weakly to moderately linked to the Engel class seizure outcome at the 12, 24 and 60 months post-surgery evaluation, but not to the seizure outcome 6 months after surgery.

Table 5: Somer´s D for correlation between seizure outcome class and number of ASM

Time	*correlation value*	*p*
6 mo	.17	.07
12 mo	.28	**.004**
24 mo	.37	**<.001**
60 mo	.29	**.05**

Note: mo = months post-surgery, Time = timing of perisurgical evaluation, bold print = significant result, ASM = antiseizure medication

3.2. Longitudinal Development of Executive Functions

3.2.1. Univariate Analysis of Planning

For univariate multilevel analysis, the measure cumulative measure 'Block Design' was used as a dependent variable to evaluate the executive function 'Planning'. Time was used as the only independent variable; no subgroups were formed. The measure 'Planning' is indicated

in scaled score points (mean = 0, standard deviation = 3). 366 values of 116 patients could be included into the model. There was a significant effect of time, $F(4, 258) = 2.84$, $p = .025$. The estimated marginal means are presented below.

Table 6: Estimated marginal means in scaled score points and standard errors for each evaluation time for Planning.

Time	Mean	*SE*
pre	9.20	0.27
6 mo	9.47	0.32
12 mo	9.64	0.29
24 mo	10.07	0.30
60 mo	9.78	0.44
Overall result	9.63	0.32

Note. pre = persurgical evaluation, mo= months post-surgery, Time = timing of perisurgical evaluation

Pairwise comparisons were conducted, comparing results of every evaluation time with the Planning performance at the presurgical evaluation as well as comparisons between consecutive evaluations. Only the difference between the performance before and 24 months after surgery was significant, showing a significant increase in Planning ability after 24 months post-surgery ($M = 10.70$, $SE = 0.30$) compared to the presurgical examination ($M = 9.20$, $SE = 0.27$), $t(256)= 3.29$, $p <.001$). 60 months after surgery, the comparison with the presurgical level was not significant anymore, the mean difference was 0.56 scaled score points.

Table 7: Planning: Pairwise comparisons of the five evaluation times

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	pre	0.26	.35
12 mo	pre	0.43	.09
24 mo	pre	0.86	**.001**
60 mo	pre	0.56	.18
6mo	pre	0.26	.35
12mo	6mo	0.17	.57
24mo	12mo	0.43	.12
60mo	24mo	-0.30	.49

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation; mo = months post-surgery, bold print = significant result, mean difference in scaled score points.

3.2.2. Univariate Analysis of Problem Solving

For univariate multilevel analysis, the cumulative measure 'Matrix reasoning' was used as a dependent variable to evaluate the executive function 'Planning'. Time was used as the only independent variable; no subgroups were formed. The measure 'Problem Solving' is indicated in scaled score points (mean = 0, standard deviation = 3). 289 values of 99 patients could be included into the model. The effect of time was not significant, $F(4, 203) = 1.54$, $p = .19$. The estimated marginal means are presented below:

Table 8: Estimated marginal means in scaled score points and standard errors for each evaluation time for Problem Solving.

Time	Mean	*SE*
Pre.	9.42	0.32
6 mo	9.62	0.40
12 mo	8.95	0.35
24 mo	9.53	0.37
60 mo	8.58	0.55
Overall result	9.22	0.40

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

Pairwise comparisons were conducted, comparing results of every evaluation time with the Problem Solving performance at the presurgical evaluation as well as comparisons between consecutive evaluations. No differences between the performance before and after surgery were significant. The difference between the performance in Problem solving at 24 months post-surgery and the performance at 60 months after surgery showed a tendency towards significance.

Table 9: Problem Solving: Pairwise comparisons of the five evaluation times

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	pre	0.20	.60
12 mo	pre	-0.47	.17
24 mo	pre	-0.58	.12
60 mo	pre	-0.84	.12
6mo	pre	0.20	.60
12mo	6mo	-0.67	.10
24mo	12mo	0.58	.12
60mo	24mo	-0.96	.09

Note. Time= timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, mean differences in scaled score points

3.2.3. Univariate Analysis of Fluency

For univariate multilevel analysis, the cumulative measure 'phonological/verbal Fluency` was used as a dependent variable to evaluate the executive function 'Fluency'. Time was used as the only independent variable; no subgroups were formed. The measure 'phonological Fluency' is indicated in standardized z-scores (mean = 0, standard deviation = 1). 245 values of 89 patients could be included into the following model. There was a significant effect of time, $F(4, 174) = 3.82$, $p = .005$. To examine this significant effect, the estimated marginal means are presented.

Table 10: Estimated marginal means in z-scores and standard errors for each evaluation time for Fluency.

Time	Mean	*SE*
pre.	-0.77	0.13
6 mo	-0.52	0.13
12 mo	-0.33	0.14
24 mo	-0.46	0.14
60 mo	-0.07	0.22

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

To analyze the evolution of Fluency over time, pairwise comparisons were conducted, comparing results of every evaluation time with the Fluency performance at the presurgical evaluation. The comparisons between the presurgical Fluency level and the performance at all postsurgical evaluations were significant: The results from the presurgical evaluation (M = -0.77, SE = 0.13) and the 6 months postsurgical evaluation (M = -0.52 , SE = 0.13) indicate that surgery and time passing resulted in an improvement $t(157)= 1.97$, $p = .050$. When comparing the results from the presurgical evaluation with those obtained at 12 months after surgery (M = -0.33, SE = 0.14) improvement was also apparent, $t(163)= 3.09$, $p = .002$, improvement also appeared when comparing the presurgical evaluation results with the 24 months postsurgical evaluation (M = -0.46, SE = 0.14; $t(162)= 2.24$, $p = .027$) and with the 60 months postsurgical evaluation (M = -0.07, SE = 0.22; $t(223)= 3.02$, $p = .003$). Consecutive evaluations showed no significant differences between each other.

Table 11: Fluency ability: Pairwise comparisons of the five evaluation times.

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	pre	0.25	**.050**
12 mo	pre	0.44	**.002**
24 mo	pre	0.31	**.027**
60 mo	pre	0.70	**.003**
12mo	6mo	0.18	0.21
24mo	12mo	-0.13	0.40
60mo	24mo	0.40	0.10

Note. Time = timing of perisurgical evaluation, pre = persurgical evaluation, mo = months post-surgery, bold print = significant result, mean differences in points of z-scores.

3.2.4. Univariate Analyses of Working Memory

3.2.4.1. Wechsler Working Memory Index. For univariate multilevel analysis, the cumulative measure 'Working Memory Index' from the Wechsler test batteries was used as a dependent variable to evaluate the executive function 'Working Memory'. Time was used as the only independent variable, no subgroups were formed. The measure 'Working Memory index' is indicated in index value points, comparable with IQ points, as used in the Wechsler Intelligence tests (mean = 100, standard deviation = 15). The values of 54 patients could be included into the following model. There was a significant effect of time, $F(4, 77.8) = 3.98$, $p = .005$. To examine this significant effect, the estimated marginal means are presented.

Table 12: Estimated marginal means in index value points and standard errors for each evaluation time for Working Memory.

Time	Mean	*SE*
pre	93.3	1.9
6 mo	88.8	2.4
12 mo	94.9	2.0
24 mo	96.9	2.1
60 mo	97.4	3.7
Overall result	94.3	2,4

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of presurgical evaluation

To analyze the evolution of the Working Memory index over time, pairwise comparisons were conducted, comparing results of every evaluation time with the Working Memory index at the presurgical evaluation. The comparisons between the presurgical Working

Memory capacities and the performance 6 months after surgery, as well as the performances 24 months after surgery were significant. Six months after surgery, the Working Memory index dropped significantly by 4.5 index value points (M = 88.82, SE = 1.93), $t(53)$= 2.16, p = .032, to then increase gradually, until reaching a significant increase 2 years after surgery of 3.6 points (M = 96.92, SE = 2,08), $t(53)$= 2.84, p = .041. 60 months after surgery, the increase was even higher, 4.1 points, however the difference was not significant, probably due to larger standard errors at this evaluation time.

Table 13: Working Memory: Pairwise comparisons of the five evaluation times.

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	pre	-4.5	**.03**
12 mo	pre	1.6	.29
24 mo	pre	3.6	**.04**
60 mo	pre	4.1	.25

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, bold print = significant result, mean difference in index value points.

3.2.4.2. *Digit Span.* For univariate multilevel analysis, the cumulative measure 'digit span' was used as a dependent variable to evaluate the executive function 'Working Memory'. Time was used as the independent variable. The measure 'digit span´ is indicated in scaled score points as used in the intelligence test batteries (mean = 10, standard deviation = 3). 322 values of 109 patients could be included into the model. The effect of time was significant, $F(4, 223) = 3.09$, p = .017. The estimated marginal means are presented below.

Table 14: Estimated marginal means in scaled score points and standard errors for each evaluation time for Digit Span

Time	Mean	*SE*
pre	8.50	0.27
6 mo	8.50	0.31
12 mo	9.01	0.29
24 mo	9.26	0.31
60 mo	9.40	0.54
Overall result	8.93	0.25

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation.

To analyze the evolution of the over time, pairwise comparisons were conducted, comparing results of every evaluation time with the Working Memory performance at the presurgical evaluation and also evaluating consecutive evaluations with each other. The comparisons between the presurgical digit span performance and the performance 12 and 24 months after surgery were significant. The evolution from 6 to 12 months after surgery showed a tendency toward significance with increasing digit span perfomance. There was a significant increase in Working Memory in the evaluation 12 months after surgery (M = 9.01, SE = 0.29) compared to the presurgical performance (M = 8.50, SE = 0.27), $t(218)$= 2.06, p = .041, also when comparing presurgical performance to the 24 months postsurgical performance (M = 9.26, SE = 0.31), $t(223)$= 2.79, p = .006.

Table 15: Working memory: Pairwise comparisons of the five evaluation times.

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	Pre	-0.01	.99
12 mo	Pre	0.51	**.041**
24 mo	Pre	0.76	**.006**
60 mo	Pre	0.88	.09
12mo	6mo	0.51	**.**07
24mo	12mo	0.25	.37
60mo	24mo	0.12	.82

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, mean difference in scaled score points.

3.2.5. Univariate Analyses of Inhibition

3.2.5.1. Go No Go-Time. For univariate multilevel analysis, the measure ‘Go No Go - time’ from the TAP test battery was used as a dependent variable to evaluate the executive function ‘Inhibition’. Time was used as the only independent variable, no subgroups were formed. The measure ‘Go No Go - time’ is indicated in T-values (mean = 50, standard deviation = 10). The values of 43 patients could be included into the model. There was no significant effect of time, $F(4, 70.87) = 0.60$, p = .67. The estimated marginal means are presented below:

Table 16: Estimated marginal means in T-values and standard errors for each evaluation time for Go No Go-Time

Time	Mean	*SE*
pre	52.7	2.1
6 mo	50.3	2.4
12 mo	54.6	2.5
24 mo	52.7	2.7
60 mo	55.1	3.5
Overall result	53.1	2.6

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

Additionally, pairwise comparisons were conducted, comparing results of every evaluation time with the Go No Go (time) performance at the presurgical evaluation. The differences between the Go No Go capacities before and after surgery were not significant.

Table 17: Go No Go-time : pairwise comparisons of the five evaluation times

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	Pre	-2.4	.42
12 mo	Pre	1.9	.52
24 mo	Pre	0.0	.99
60 mo	Pre	2.5	.53

Note.Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, mean difference in T-values.

3.2.5.2. Go No Go–Errors. For another univariate multilevel analysis, the measure ‘Go No Go - errors’ from the TAP test battery was used as a dependent variable to evaluate the executive function ‘Inhibition’. Time was used as the only independent variable; no subgroups were formed. The measure ‘Go No Go - errors’ is indicated in T-values (mean = 50, standard deviation = 10). The values of 42 patients could be included into the model. There was no significant effect of time, $F(4, 67.89) = 0.45$, $p = .77$. The estimated marginal means are presented below:

Table 18: Estimated marginal means in T-values and standard errors for each evaluation time for Go-No-Go-Errors.

Time	Mean	*SE*
pre	46.1	1.9
6 mo	47.1	2.2
12 mo	47.9	2.3
24 mo	47.1	2.3
60 mo	50.5	3.1
Overall result	47.7	2.4

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

Additionally, pairwise comparisons were conducted, comparing results of every evaluation time with the Go No Go - errors performance at the presurgical evaluation. The differences between the Go No Go capacities before and after surgery were not significant.

Table 19: Go No Go- errors: pairwise comparisons of the five evaluation times.

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	pre	1.0	.71
12 mo	pre	1.8	.50
24 mo	pre	1.0	.70
60 mo	pre	4.4	.20

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, mean differences in T-values.

3.2.5.3. D2- KL. For univariate multilevel analysis, the cumulative measure ‘D2- KL’ was used as a dependent variable to evaluate the executive function ‘Inhibition’. Time was used as the only independent variable, no subgroups were formed. The measure ‘D2- KL´ is indicated in standard scores (mean = 100, standard deviation = 10). 126 values of 53 patients could be included into the model. There was no significant effect of time, $F(4, 77) = 1.83$, $p = .13$. The estimated marginal means are presented below:

Table 20: Estimated marginal means in standard scores and standard errors for each evaluation time for D2-KL

Time	Mean	*SE*
pre	100.56	1.79
6 mo	103.30	1.87
12 mo	102.92	1.96
24 mo	104.74	1.93
60 mo	104.82	2.27
Overall result	103.27	1.52

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluatio

Pairwise comparisons were conducted, comparing results of every evaluation time with the Inhibition performance at the presurgical evaluation and between consecutive evaluations. There was a significant increase in Inhibition capacity over time after 24 months (*M*= 104.74, *SE*= 1.93) compared to the presurgical examination (*M*= 100.56, *SE*= 1.79), *t* (76) = 2.40, *p* = .019. A tendency towards significance was shown between the presurgical and the 6 months postsurgical evaluation as well as between the presurgical and the 60 months postsurgical evaluation.

Table 21: D2-KL: pairwise comparisons of the five evaluation times.

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	Pre	2.74	.09
12 mo	Pre	2.36	.18
24 mo	Pre	4.17	**.019**
60 mo	Pre	4.26	.06
12 mo	6 mo	-0.38	.83
24 mo	12 mo	1.81	.33
60 mo	24 mo	0.09	.97

Note. Time = timing of presurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, bold print = significant result, mean difference in standard scores.

3.2.6. Univariate Analyses of Monitoring

3.2.6.1. Divided Attention – Errors. For univariate multilevel analysis, the measure 'divided attention- errors' from the TAP test battery was used as a dependent variable to evaluate the executive function 'Monitoring'. Time was used as the only independent variable, no subgroups were formed. The measure 'divided attention- errors' is indicated in T-values (mean = 50, standard deviation = 10). The values of 19 patients could be included into the model. There was no significant effect of time, $F(4, 21.75) = 0.35$, $p = .84$. The estimated marginal means are presented below:

Table 22: Estimated marginal means in T-values and standard error for each evaluation time for Divided Attention- Errors.

Time	Mean	*SE*
pre	50.4	2.6
6 mo	51.6	2.8
12 mo	53.5	2.8
24 mo	53.7	3.1
60 mo	54.1	4.7
Overall result	55.7	3.2

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

Pairwise comparisons were conducted, comparing results of every evaluation time with the divided attention performance at the presurgical evaluation. The differences between the performance before and after surgery were not significant. Again, lack of power due to small sample size could explain the non-significance of the results.

Table 23: Divided attention-errors: pairwise comparisons of the five evaluation times

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	Pre	1.2	.72
12 mo	Pre	3.0	.37
24 mo	Pre	3.3	.37
60 mo	Pre	3.6	.47

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, mean differences in T-values.

3.2.7. Univariate Analyses of Flexibility

3.2.7.1. TMT B -Time. For univariate multilevel analysis, the measure 'Trail Making Test Part B (time)' was used as a dependent variable to evaluate the executive function 'flexiblity'. Time was used as the only independent variable; no subgroups were formed. The measure 'TMT B' is indicated in standardized z-scores (mean = 0, standard deviation = 1). The values of 19 patients could be included into the model. There was no significant effect of time, $F(4, 6.19) = 1.76$, $p = .25$. The estimated marginal means are presented below:

Table 24: Estimated marginal means in z-scores and standard errors for each evaluation time for TMT B-Time.

Time	Mean	*SE*
pre.	-0.30	0.59
6 mo	-0.92	0.77
12 mo	-1.00	0.83
24 mo	-2.11	0.72
60 mo	-0.27	0.79
Overall result	-0.92	0.74

Note. Pre = presurgial evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

Pairwise comparisons were conducted, comparing results of every evaluation time with the TMT B performance at the presurgical evaluation. Only the difference between the performance before and 24 months after surgery was significant, showing a decrease of Flexibility performance in time ($M = -2.11$, $SE = 0.72$), $t(18) = 1.58$, $p = .043$. 60 months after

surgery, the comparison with the presurgical level was not significant anymore, the mean difference was 0.03 in standardized z-scores.

Table 25: TMT B- Time: pairwise comparisons of the five evaluation times

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	Pre	-0.62	.40
12 mo	Pre	-0.70	.41
24 mo	Pre	-1.81	**.04**
60 mo	Pre	0.03	.97

Note. Time = timing of persisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, bold print = significant results, mean differences in points in z-scores.

3.2.7.2. Symbol Search. For univariate multilevel analysis, the cumulative measure 'symbol search' was used as a dependent variable to evaluate the executive function 'flexiblity'. Time was used as the only independent variable; no subgroups were formed. The measure 'symbol search′ is indicated in scaled score points as used in the Wechsler test batteries (mean = 10, standard deviation = 3). 145 values of 58 patients could be included into the model. There was no significant effect of time, $F(4, 105) = 0.42$, $p = .79$. The estimated marginal means are presented below:

Table 26: Estimated marginal means in scaled score points and standard errors for each evaluation time for Symbol Search

Time	Mean	*SE*
Pre	9.83	0.47
6 mo	9.96	0.57
12 mo	10.29	0.49
24 mo	10.24	0.51
60 mo	9.27	1.02
Overall result	9.92	1.02

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

Pairwise comparisons were conducted, comparing results of every evaluation time with the Flexibility performance at the presurgical evaluation and between consecutive evaluations. None of the comparisons was significant.

Table 27: Symbol Search: pairwise comparisons of the five evaluation times

(I) Time	(J) Time	Mean Difference (I-J)	*p*
6 mo	Pre	0.14	.82
12 mo	Pre	0.47	.35
24 mo	Pre	0.41	.45
60 mo	Pre	-0.56	.92
12 mo	6 mo	0.33	.58
24 mo	12 mo	-0.06	.92
60 mo	24 mo	-0.97	.38

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, mean differences in scaled score points.

3.2.8. Summary of Univariate Models of EF

The following Table gives an overview of the different univariate multilevel models for each EF presented in this chapter.

Table 28: Univariate multilevel models: Significance of the effect of time on Executive Functions

Executive functions	Significant effect of time
Planning	✓*
Problem Solving	x
Fluency	✓**
Working Memory	
Wechsler Working Memory Index	✓**
Digit span	✓*
Inhibition	
TAP Go No Go- Time	x
TAP Go No Go- Errors	x
D2-KL	x
Monitoring	x
Flexibility	
Trail Making Test B- Time	x
Symbol Search	x

Note. x = no significant effect of time; ✓ = significant effect of time: * $p < 0.05$, ** $p < 0.01$

3.3. Multivariate Analyses of EF

3.3.1. Multivariate Analysis of Planning

The executive function 'Planning' was evaluated using the cumulative measure 'Block Design' as a dependent variable, and time as well as other predictors as independent variables (IV). The measure Planning is indicated in scaled score points with a mean at 10, and a standard deviation of 3. 366 values of 116 patients could be included into the following models.

3.3.1.1. IV presurgical IQ. There was no significant main effect of time, $F(4, 260) = 0.30$, $p = .88$. There was also no significant effect of the interaction time x presurgical IQ on Planning capacities, $F(4, 260) = 0.60$, $p = .66$. However, there was a significant main effect of presurgical IQ on Planning, $F(1, 123) = 66.42$, $p = <.001$. The F-Tests for the main and interaction effects are reported in the following table:

Table 29: F-Tests for fixed effects Time, Presurgical IQ and their interaction in Planning

Source	*F*	$df_{Nom.}$	$df_{Dom.}$	*p*
Time	0.30	4	260	.88
Persurgical IQ	66.42	1	123	**<.001**
Time x Presurgical IQ	0.60	4	260	.66

Note. Bold print = significant result

Because presurgical IQ is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 30: Regression coefficient ´presurgical IQ´ in Planning for the different evaluation times

Time	*β*	*p*
presurgical IQ = baseline	1.07	**<.001**
6 months	1.08	
12 months	1.08	
24 months	1.10	
60 months	1.10	

To calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is 1.07, which is significant, $t = 6.03$, $p = <.001$. This means that at the presurgical evaluation, the higher the IQ, the higher is the performance at the Planning task. The regression coefficient tells us that with every IQ point difference, the Planning performance increases by 1.07 scaled score points. The influence of

presurgical IQ varies only minimally across evaluation times: At the 6 months postsurgical evaluation, the Planning ability is 1.08 scaled score points higher per IQ point increase. At 12 months after surgery the Planning ability is also 1.08 scaled score points higher with every IQ point increase, at 24 months it's 1.10 scaled score points more per additional IQ point and at 60 months after surgery it's also 1.10 scaled score points increase per additional IQ point.

3.3.1.2. IV Side of Surgery. The main effect of time was significant, $F(4, 254) = 2.74$, $p = .029$. Neither the effect for the side of surgery, on which surgery was performed, nor the interaction Time x side of surgery reached significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 31: F-Tests for fixed effects time, side of surgery and their interaction in Planning

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.74	4	254	**.029**
side of surgery	2.30	1	128	.13
Time x side of surgery	0.50	4	254	.74

Note. Bold print = significant result

The overall F-Test showed no significant differences when comparing the means of the 5 evaluation times, neither for the right nor for the left hemisphere.

Table 32: Overall F-Test results of time for every side of surgery in Planning

side of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
right	1.05	4	255	.38
left	2.21	4	252	.07

To examine the significant effect of time, the estimated marginal means are presented in the Appendix 4. Simple contrasts revealed no significant differences between groups at any time, when comparing patient groups, which had surgery either on the left or right hemisphere, at each evaluation time (Appendix 4). Pairwise comparisons were conducted to analyze the evolution of Planning capacities over time, in regard of the hemisphere on which surgery was performed (Appendix 4). For the right hemisphere operated group, there were no significant changes over time, for the left sided operated group, there was a significant increase in scaled score points between the preoperative evaluation and the evaluation 24 months after surgery of 1.06 scaled score points, $t(252) = -2.78$, $p = .006$. When comparing the different evaluation times in consecutive order, no significant differences could be observed (i.e. 12 months post-surgery. to 24 months post-surgery, $t(248) = -.736$, $p = .059$ for left sided surgery patients).

3.3.1.3. IV Etiology. The effects of etiology, time, and interaction Time x etiology did not reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 33: F-Tests for fixed effects time, etiology and their interaction in Planning

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.56	4	233	.19
etiology	1.96	6	125	.08
Time x etiology	1.05	20	234	.41

However, at the 60 months post-surgery evaluation, there were significant differences between the etiology groups, shown in the overall F-tests. Also, only the tumor group showed significant differences when comparing the means of all the testing times for each etiology feature.

Table 34: Overall F-Test results of etiology for every evaluation time in Planning

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.42	6	204	.87
6 mo	1.59	5	309	.16
12 mo	1.33	5	255	.25
24 mo	1.77	5	264	.12
60 mo	2.34	5	335	**.042**

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Table 35: Overall F-test results of time for every etiology type in Planning

etiology	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
MCD	0.97	4	234	.42
tumor	3.47	4	237	**.009**
dual pathology	0.96	4	235	.43
vascular malformation	0.40	3	232	.75
gliosis	0.54	4	235	.71
mesial temporal sclerosis	1.63	4	230	.17
other	0.69	1	224	.41

Note. Bold print = significant result, MCD = malformation of cortical development

To further analyze these findings, the marginal means are presented in the Appendix 4. Deviation contrasts were conducted to analyze the Planning capacities for all etiology groups at the 5 testing times (Appendix 4). Deviation contrasts were used to compare all of the 6 features of etiology with the mean of all features combined. Only two deviation contrasts, both

of the gliosis group, were significant. This group had significantly lower performance in Planning 12 months after surgery: Its mean was 2.4 scaled score points under the mean of the whole surgery cohort, $t(221) = -2.31$, $p = .022$. At 60 months post-surgery, its mean was even 3.9 scaled score points under the mean of the surgery cohort, $t(328) = -2.13$, $p = .034$.

To analyze the development of Planning abilities for the different etiology groups, from the presurgical evaluation up to 5 years after surgery, pairwise comparisons were conducted (Appendix 4). Only the tumor group differed significantly across testing times: There was a significant increase of 1.69 scaled score points between the presurgical and the 24 months post-surgical evaluation, $t(235) = -3.41$, $p = .001$, as well as a significant increase of 2.17 scaled score points between the presurgical and the 60 months post-surgical evaluation, $t(243) = -2.31$, $p = .022$. However, the increase in consecutive order from presurgical evaluation to the 6 months post-surgical evaluation, then to 12 months, 24 months and 60 months after surgery was not significant.

3.3.1.4. IV Surgery Type. In the F-tests for fixed effects, the effects of surgery type, time, and interaction Time x surgery type did not reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 36: F-Tests for fixed effects time, surgery type and their interaction in Planning

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.87	4	238	.12
Surgery type	2.12	5	117	.07
Time x surgery type	0.56	19	239	.93

Table 37: Estimated marginal means in scaled score points and standard errors for each evaluation time and for every surgery type in Planning.

Time	type of surgery	*Mean*	*SE*
pre	lesionectomy	9.82	0.55
	intralobar tailored resection	8.41	0.47
	multilobar tailored resection	8.81	0.63
	AHE	10.67	1.66
	standard temporal resection ± AHE	9.73	0.75
	temporal tailored resection + AHE	9.94	0.85
6 mo	lesionectomy	10.54	0.60
	intralobar tailored resection	8.71	0.57
	multilobar tailored resection	8.31	0.73

	AHE	9.17	1.84
	standard temporal resection ± AHE	10.45	0.89
	temporal tailored resection + AHE	10.38	1.19
12 mo	lesionectomy	10.89	0.58
	intralobar tailored resection	8.89	0.50
	multilobar tailored resection	9.08	0.70
	AHE	10.67	1.66
	standard temporal resection ± AHE	9.80	0.81
	temporal tailored resection + AHE	9.46	0.90
24 mo	lesionectomy	10.91	0.59
	intralobar tailored resection	9.33	0.52
	multilobar tailored resection	9.10	0.72
	AHE	12.00	1.66
	standard temporal resection ± AHE	10.98	0.81
	temporal tailored resection + AHE	9.89	1.09
60 mo	lesionectomy	10.34	0.89
	intralobar tailored resection	8.97	0.82
	multilobar tailored resection	9.10	0.93
	AHE	13.65	2.30
	standard temporal resection ± AHE	10.35	1.13

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation, AHE = amygdalohippocampectomy

To further analyze the Planning abilities for all surgery groups at the 5 testing times, deviation contrasts were conducted (Appendix 4). The 6 features of surgery type were compared with the mean of all features combined, for each of the testing times. Only at the presurgical testing, the intralobar tailored resection group differed significantly, with 1.16 scaled score points less than the mean of the cohort, $t(179) = -2.16$, $p = .032$. All other deviation contrasts were not significant.

Pairwise comparisons for each surgery group were conducted (Appendix 4). The lesionectomy group differed significantly with an increase of 1.10 scaled score points between the pre surgical and the 12 month post-surgical evaluation, $t(235) = -2.08$, $p = .038$, as well as with an increase of also 1.10 scaled score points between the pre surgical and the 24 months post-surgical evaluation, $t(238) = -2.05$, $p = .042$. The increase in consecutive order from presurgical evaluation to the 6 months post-surgical evaluation, then to 12 months, 24 months and 60 months after surgery was not significant. The intralobar tailored resection group had a significant increase of 0.93 scaled score points between pre surgical and 24 months post-

surgical evaluation, $t(234) = -2.03$, $p = .043$. All other pairwise comparisons for this group as well as for the other surgery groups were not significant.

3.3.1.5. IV Localization. The effect of time was significant as well as the effect of localization of the surgery, but not the interaction effect time x localization. The F-Tests for the main and interaction effects are reported in the following table:

Table 38: F-Tests for fixed effects of time, localization of surgery and their interaction in Planning

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.970	4	236	**.020**
localization	2.503	5	113	**.034**
Time * localization	.564	17	238	.916

Note. Bold print = significant result.

However, the overall F-test results of time showed no significant differences between testing times for any localization subgroup.

Table 39: Overall F-Test Results of time for every localization group in Planning

localization	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
frontal	1.63	4	239	.17
temporal	0.83	4	245	.51
parietal	0.68	4	238	.61
occipital	1.27	3	231	.29
insular	1.34	2	229	.26
multilobar	0.39	4	242	.81

The overall F-Test of localization showed significant differences in Planning performances 6 months after surgery when comparing the groups, at other testing times, no significant differences were shown.

Table 40: Overall F-Test Results of localization for every evaluation time in Planning

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	1.88	5	217	.10
6 mo	2.30	5	279	**.045**
12 mo	1.81	5	246	.11
24 mo	1.31	4	284	.27
60 mo	1.30	3	339	.27

Note: pre = presurgical evaluation

Estimated marginal means are presented in a table in the Appendix 4. Deviation contrasts were conducted to analyze the Planning capacities for all localization groups at the 5 testing times. Only one deviation contrast was significant. The frontal localization group had significantly lower performance in Planning 12 months after surgery: It's mean was 1.47 scaled score points under the mean of the whole surgery cohort, $t(195) = -1.99$, $p = .048$.

As before, pairwise comparisons were conducted to analyze the development of the Planning capacities for the different localization groups, from the presurgical evaluation up to 5 years after surgery. The detailed results can be seen in Appendix 4. The temporal, parietal, occipital, insular und multilobar subgroups had no significant variation in Planning capacities over time. The frontal subgroup had a significant increase of 1.21 scaled score points between the presurgical and the 24 months post-surgical evaluation, $t(239) = -2.504$, $p = .013$. The increase from presurgical evaluation to the 6 months post-surgical evaluation, then to 12 months and 24 months after surgery were not significant.

3.3.1.6. IV Age at Onset. There was a significant interaction effect of time x age at onset, $F(4, 258) = 3.34$, $p = .010$. Also, there was a significant effect of age at epilepsy onset, $F(1, 137) = 8.43$, $p < .001$. The effect of time did not reach significance, $F(4, 253) = 2.11$, $p = .080$, but a tendency towards significance. The influence of age at onset on the Planning abilities varies over time. The overall F-test result for time is also significant, $F(4, 254) = 3.612$, $p = .007$. Because age at onset is a metric variable no estimated marginal means can be calculated for it, instead the regression coefficient is interpreted:

Table 41: Regression Coefficient `age at onset´ for the 5 evaluation times in Planning

Time	*β*	*p*
presurgical IQ = baseline	0.07	.27
6 months	0.07	
12 months	0.09	
24 months	0.10	
60 months	0.47	

To calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is .067, which is not significant, $t = 5.04$, $p = .27$. This means that at the presurgical evaluation, with every year a patient is older at onset of epilepsy, its Planning ability is .067 scaled score points higher. The influence of the age at onset of epilepsy on Planning ability increases slightly across evaluation times: At the 6

months postsurgical evaluation, the Planning ability is 0.07 scaled score points higher for every year a patient is older at onset. At 12 months after surgery the Planning ability is 0.09 scaled score points higher with every year, at 24 months it's 0.10 scaled score points more per year older at the start of epilepsy, and at 60 months after surgery it's 0.47 scaled score points increase per year older at onset.

3.3.1.7. IV Duration of Epilepsy (in Years). A significant effect of time, $F(4, 256) = 3.66$, $p = .006$ was revealed. Neither the duration of epilepsy nor the interaction Time x duration of epilepsy reached significance, meaning time influences the patients Planning capacity independently of the duration of epilepsy before surgery. The F-Tests for the main and interaction effects are reported in the following table:

Table 42: F-tests for fixed effects Time, Duration of epilepsy and their interaction in Planning

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	3.66	4	256	**.006**
Duration of epilepsy (in years)	3.38	1	156	.07
Time *duration of epilepsy	1.92	4	259	.11

Because duration of epilepsy is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 43: Regression coefficient ´duration of epilepsy´ for Planning for the 5 evaluation times

Time	*β*	*p*
presurgical IQ = baseline	-.04	.51
6 months	-.05	
12 months	-.01	
24 months	-.14	
60 months	-.30	

As in the independent variable 'age at onset of epilepsy', to calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is -.04, which is not significant, $t = -0.67$,
$p = .51$. This means that at the presurgical evaluation, the Planning ability is .04 scaled score points lower for every additional year of epilepsy duration prior to surgery. The influence of the duration of the illness varies only a little across evaluation times: At the 6 months postsurgical evaluation, the Planning ability is 0.05 scaled score points lower for every year a

patient has been having epilepsy. At 12 months after surgery Planning is just 0.01 scaled score points lower with every year, at 24 months it's 0.14 scaled score points less per year of epilepsy, and at 60 months after surgery it's 0.30 scaled score points decrease per year of epilepsy duration.

3.3.1.8. IV Seizure Outcome. There was no significant effect of time, only a tendency toward significance, and no significant effect of the Seizure outcome (categories Engel 1a, Engel >1a) or of its interaction. The F-Tests for the main and interaction effects are reported in the following table:

Table 44: F-Tests for fixed effects Time, Seizure outcome (in Engel categories) and their interaction in Planning

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.59	3	247	.05
Engel	2.00	1	293	.16
Time * Engel	0.61	3	249	.61

Since the seizure outcome only has 2 features, no overall F-Test was reported, because it is the same as the F-tests for main effects. The estimated marginal means are presented in the Appendix 4. Simple contrasts were conducted to analyze the evolution of the Planning abilities over time, in regard of the seizure outcome of the patients (Appendix 4). Statistically, there were no significant differences in Planning abilities between the two patient groups across evaluation times, whether they still had epileptic seizures after surgery (group '>1a') or not (group '1a').

Other pairwise comparisons, comparing the performance at the 5 evaluation times for each group separately, were conducted (Appendix 4). When comparing the 5 evaluation times in consecutive order, no significant differences could be observed, neither for the seizure free (1a), nor for the group of patients which still had seizures (>1a).

Table 45: Simple contrasts between seizure outcome groups for each evaluation time in Planning.

Time	Engel outcome Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
6 mo	1a - > 1a	1.09	0.59	1.85	272	.07
12 mo	1a - > 1a	0.57	0.47	1.23	277	.22
24 mo	1a - > 1a	0.27	0.47	0.58	273	.56
60 mo	1a - > 1a	0.02	0.80	0.02	255	.98

Table 46 : Pairwise comparisons between consecutive evaluation times for each seizure outcome group in Planning.

Engel outcome	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
1a	6 mo - 12 mo	-0.12	0.35	-0.34	246	.74
	12 mo - 24 mo	-0.38	0.34	-1.11	240	.27
	24 mo - 60 mo	0.36	0.61	0.58	249	.56
>1a	6 mo - 12 mo	-0.63	0.58	-1.09	250	.28
	12 mo - 24 mo	-0.68	0.47	-1.44	245	.15
	24 mo - 60 mo	0.10	0.64	0.16	249	.87

Note. mo = months post-surgery

3.3.1.9. IV Antiseizure Drug (ASM) Load. The effect of antiseizure drug load was statistically significant, $F(2, 297) = 4.023$, $p = .019$. However, there were no significant effects of time or of its interaction Time x ASM load. The F-Tests for the main and interaction effects are reported in the following table:

Table 47: F-Tests for fixed effects Time, antiseizure drug load and their interaction in Planning

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.04	4	255	.39
ASM load	4.02	2	297	**.02**
Time x ASM load	1.33	7	257	.24

The overall F- test shows a significant difference between the different ASM load groups at 24 months after surgery, but not at other evaluation times.

Table 48: Overall F-Test results of antiseizure drug load for every evaluation time in Planning

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	.09	2	288	.91
6 mo	.62	1	276	.43
12 mo	1.44	2	271	.24
24 mo	3.79	2	270	**.024**
60 mo	2.65	2	254	.07

Note. pre = presurgical evaluation, mo = months post-surgery

The estimated marginal means are presented in the Appendix 4. Pairwise comparisons were conducted to analyze the evolution of the Planning abilities over time. Significant

differences in Planning between patients' ASM groups happened at 24 months and tendency towards significance at 60 months after surgery. At 24 month after, there were significant differences between patients taking no ASM and patients taking more than 1 ASM, $t(279) = 2.10$, $p = .04$, as well as between patients taking 1 and patients taking more than 1 ASM, $t(270) = 2.66$, $p = 0.08$. At 24 months after surgery, patients taking more than 1 ASM had 1.28 scaled score points less than those taking no ASM, and 1.43 scaled score points less than those taking 1 ASM. At 60 months post-surgery, there was still a significant effect when comparing patients who took 1 ASM versus patients who were taking more than 1 ASM. On average, patients with more than 1 ASM had 2.07 scaled score points less in Planning capacities than patients taking just 1 ASM. All other comparisons between patients ASM groups at different evaluation times revealed no significant differences.

Table 49 : Pairwise comparisons of Planning scores between the antiseizure drug load groups for every evaluation time

Time	ASM Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
	0 - 1	-0.36	1.48	-0.24	286	.81
pre	0 - > 1	-0.48	1.46	-0.33	289	.74
	1 - > 1	-0.13	.43	-0.30	289	.77
6 mo	1 - > 1	0.39	.49	0.79	276	.43
	0 - 1	0.28	.89	0.32	260	.75
12 mo	0 - > 1	1.00	.93	1.08	267	.28
	1 - > 1	0.72	.45	1.58	281	.11
	0 - 1	-0.14	.53	-0.27	265	.79
24 mo	0 - > 1	1.28	.61	2.10	279	**.036**
	1 - > 1	1.43	.54	2.66	270	**.008**
	0 - 1	-0.66	1.08	-0.62	246	.54
60 mo	0 - > 1	1.40	1.13	1.24	252	.22
	1 - > 1	2.07	.90	2.29	262	**.023**

Note. ASM = antiseizure drug load groups, pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

Other pairwise comparisons, comparing the performance at the 5 evaluation times for each ASM group separately, were not conducted, since these did not make sense: it was expected for most patients to change ASM groups with passing time, when ASM were weaned off after a seizure free period following surgery.

3.3.2. Multivariate Analysis of Problem Solving

The executive function 'Problem Solving' was investigated with the cumulative measure 'Matrix reasoning', using the previous set of epilepsy- and epilepsy surgery related variables and time as predictors. The measure 'Problem Solving' is indicated in scaled scores as used in the Wechsler Intelligence tests, with the mean at 10, and a standard deviation of 3. 289 values of 99 patients could be included into the following models.

3.3.2.1. IV Presurgical IQ. As in other dependent variables, there was no significant main effect of time, $F(4, 211) = 0.69$, $p = .60$. There was also no significant effect of the interaction time x presurgical IQ on Problem Solving capacities, $F(4, 211) = 0.88$, $p = .48$. Again, there was a significant main effect of presurgical IQ, $F(1, 111) = 53.77$, $p = <.001$. The F-Tests for the main and interaction effects are reported in the following table:

Table 50: F-Tests for fixed effects Time, Presurgical IQ and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.69	4	211	.60
Persurgical IQ	53.77	1	111	**<.001**
Time x Presurgical IQ	0.88	4	211	.48

Note. Bold print = significant result

Because presurgical IQ is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 51: Regression coefficient ´presurgical IQ´ in Problem Solving for the 5 evaluation times

Time	*β*	*p*
presurgical IQ = baseline	0.13	**<.001**
6 months	0.12	
12 months	0.15	
24 months	0.15	
60 months	0.08	

As for the IV Planning, to calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is 0.13, which is significant, $t = 6.1$, $p = <.001$. This means that at the presurgical evaluation, the higher the IQ, the higher is the performance at reasoning. The regression coefficient signifies

that with every IQ point difference, the reasoning performance increases by 0.13 scaled score points points. The influence of presurgical IQ varies across evaluation times: At the 6 months postsurgical evaluation, the reasoning ability is 0.12 scaled score points higher per IQ point increase. At 12 months after surgery the reasoning ability is 0.15 scaled score points higher with every additional IQ point, at 24 months it's also 0.15 scaled score points more per additional IQ point and at 60 months after surgery it's 0.08 scaled score points increase per additional IQ point.

3.3.2.2. IV Side of Surgery. There was a significant effect of side of surgery, $F(4, 200) = 5.74$, $p = .018$. Neither the effect of time nor the interaction Time x side of surgery reached significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 52: F-Tests for fixed effects time, side of surgery and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.56	4	200	.19
Side of surgery	5.74	1	110	**.018**
Time x side of surgery	0.14	4	200	.97

Note. Bold print = significant result

The overall F-tests of time showed no significant differences between results at the 5 evaluations, within each group. The overall F-Tests of side of surgery revealed no significant differences between the left and the right hemisphere group for any testing time. However, at 3 out of 5 evaluation times, the significance level showed a tendency towards significance ($p < .1$).

Table 53: Overall F-Test results of time for every side of surgery in Problem Solving

Side of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Right	0.86	4	200	.49
Left	0.88	4	199	.48

Table 54: Overall F-Test results of side of surgery for every evaluation time in Problem Solving

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	3.16	1	180	.08
6 mo	3.15	1	260	.08
12 mo	2.22	1	213	.14
24 mo	3.58	1	229	.06
60 mo	2.36	1	276	.13

Note. Pre = presurgical evaluation, mo = months post-surgery

To examine the significant effect of the side of surgery on which surgery was performed, the estimated marginal means are presented in the Appendix 5. Pairwise comparisons were done in order to evaluate the evolution of Problem Solving abilities over time, for each side of surgery group separately. All analyses were not significant, showing no accelerated increase or decrease of Problem Solving capacities over time (Appendix 5).

3.3.2.3. IV Etiology. The effect of etiology did reach significance, $F(5, 106) = 2.88$, $p = .018$. The effects for time and interaction Time x etiology did not reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 55: F-Tests for fixed effects time, etiology and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.30	4	183	.87
Etiology	2.88	5	106	**.018**
Time x etiology	1.47	18	183	.11

The overall F-test of time showed significant differences within both the MCD group and the mesial temporal sclerosis group, when comparing all evaluation times.

Table 56: Overall F-test results of time for every etiology type in Problem Solving

Etiology	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
MCD	3.31	4	182	**.012**
Tumor	0.31	4	184	.87
dual pathology	0.60	4	181	.66
vascular malformation	0.26	3	176	.85
Gliosis	0.37	3	190	.78
mesial temporal sclerosis	3.38	4	183	**.011**

Note. Bold print = significant result, MCD = malformation of cortical development

The overall-F tests for etiology revealed significant differences between etiology groups at 12 months after surgery and at the 60 months post-surgery evaluation.

Table 57: Overall F-Test results of etiology for every evaluation time in Problem Solving

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	2.01	5	201	.08
6 mo	1.52	5	261	.18
12 mo	3.65	5	252	**.003**
24 mo	1.83	5	261	.11
60 mo	2.79	3	261	**.040**

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

To examine the significant effect of etiology, the estimated marginal means were calculated (Appendix 5). Deviation contrasts were conducted to analyze the Problem Solving capacities for the different etiologies at the 5 testing times in comparison to the mean of the cohort. The detailed results can be seen in Appendix 5. At the presurgical evaluation, only the mesial temporal sclerosis group differed significantly from the cohort, by an estimated 3.27 scaled score points under the mean of the cohort, $t(185) = -2.23$, $p = .027$. The tumor group showed a tendency towards significance, $t(164) = 1.96$, $p = .05$. 6 months after surgery this group still deviated from the mean by 3.03 scaled score points, but the difference was not statistically significant, and it did not differ significantly after that at other testing times. Other groups did not differ significantly at presurgical evaluation, neither at the 6months post-surgery evaluation. 12 months and 60 months after surgery, the MCD group reached significantly lower results than the mean of the cohort, $t(216) = -2.97$, $p = .003$ and $t(260) = -2.88$, $p = .004$, estimated at 2.25 and 2.40 scaled score points less.

Pairwise comparisons allowed to see the evolution of Problem Solving capacities over time, within each etiology group. The detailed results can be seen in the Appendix 5. For the MCD subgroup, there was a significant decrease of 1.41 scales score points between pre surgery and 12 months post-surgery, $t(184) = 2.67$, $p = .008$. When looking at the consecutive evolution of scores, there was no significant change between presurgical evaluation and evaluation 6 months after surgery, but there was a significant decrease of 1.17 scaled score points between 6months and 12 months after surgery, $t(179) = 2.02$, $p = .045$. Also, when comparing the presurgical capacities with the capacities in the long-term, 60 months after surgery, a significant decrease of 2.02 scaled score points could be noted, $t(184) = 2.84$, $p = .005$. Significant changes also happened in the mesial temporal sclerosis group: Significant increases of 5 and 4.81 scaled

score points could be noted on the longer term, between the presurgical capacities and the capacities 24 months and 60 months after surgery, $t(169) = -3.13$, $p = .002$ and $t(1200) = -2.76$, $p = .006$. No significant changes in scaled scores for Problem Solving capacities were found for the tumor group, the dual pathology group, the vascular malformation group or the gliosis group. For the vascular malformation group and the gliosis group there was no data available at the evaluation 60 months after surgery.

3.3.2.4. IV Surgery Type. The effects of surgery type, time, and interaction Time x surgery type did not reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 58: F-Tests for fixed effects time, surgery type and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.34	4	194	.85
Surgery type	1.48	5	101	.20
Time x surgery type	1.35	20	179	.15

The overall F-Tests of time revealed significant differences of results at different testing times within the AHE group.

Table 59: Overall F-Test Results of time for every surgery type in Problem Solving

type of surgery	*F*	df_{Nom}	df_{Denom}	*p*
Lesionectomy	0.95	4	174	.44
intralobar tailored resection	1.13	4	185	.34
multilobar tailored resection	0.60	4	180	.66
AHE	3.49	4	170	**.009**
standard temporal resection ±AHE	0.87	4	176	.48
temporal tailored resection + AHE	1.25	4	192	.29

Note. AHE = amygdalohippocampectomy.

The estimated means can be seen in Appendix 5. To further analyze the Problem Solving abilities for all surgery groups at the 5 testing times, deviation contrasts were conducted. Only at the 24 months post-surgery testing, the temporal tailored resection + AHE group differed significantly, with 3.35 scaled score points less than the mean of the cohort, $t(259) = -2.16$ $p = .032$. All other deviation contrasts were not significant.

Pairwise comparisons for each surgery group were conducted. The AHE group differed significantly with an increase of 6 scaled score points between the pre surgical and the 24 month

post-surgical evaluation, $t(166) = -3.02$, $p = .003$, as well as with an increase of also 6 scaled score points between the pre surgical and the 60 months post-surgical evaluation, $t(166) = -3.02$, $p = .003$. The increase in consecutive order from presurgical evaluation to the 6 months post-surgical evaluation, then to 12 months, 24 months and 60 months after surgery was not significant. All other pairwise comparisons for the other surgery groups were not significant.

3.3.2.5. IV Localization. The effect of localization of surgery was significant, but not the effect of time or of the interaction time x localization. The F-Tests for the main and interaction effects are reported in the following table:

Table 60: F-Tests for fixed effects of time, localization of surgery and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.60	4	175	.66
Localization	2.38	5	91	**.045**
Time x localization	1.31	18	178	.19

Note. Bold print = significant result

The overall F-test of localization showed a significant difference between localization groups at 24 months post-surgery. The overall F-test of time revealed significant differences across evaluations in the parietal group.

Table 61: Overall F-Test Results of localization for every evaluation time in Problem Solving

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.79	5	192	.56
6 mo	0.55	4	261	.70
12 mo	2.22	5	210	.05
24 mo	3.46	5	238	**.005**
60 mo	1.42	4	261	.23

Note: pre = presurgical evaluation

Table 62: Overall F-Test Results of time for every localization group in Problem Solving

localization	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
frontal	1.20	4	180	.31
temporal	1.30	4	188	.27
parietal	2.95	4	181	**.021**
occipital	0.05	3	169	.99
insular	1.93	3	167	.13
multilobar	0.60	4	181	.66

To examine the significant effect of localization, the estimated marginal means are presented in a table in the Appendix 5. Deviation contrasts were conducted to analyze the Problem Solving skills for all localization groups at the 5 testing times. Only the parietal group differed significantly from the mean of the cohort, at 12 months and at 24 months post-surgery, $t(170) = 2.56$, $p = .011$ and $t(251) = 3.16$, $p = .002$, but not anymore at 60 months after surgery, $t(225) = .64$, $p = .53$. At 12 months after surgery the parietal group had on average 3.26 scaled score points less than the mean of the cohort, and at 24 months after surgery it had 5.16 scaled score points less. At 60 months after surgery however, the parietal group differed non-significantly from the mean of the cohort, by only .92 scaled score points less.

Pairwise comparisons were conducted to analyze the development of the Problem Solving capacities for the different localization groups, from the presurgical evaluation up to 5 years after surgery. The detailed results can be seen in Appendix 5. The frontal, occipital und multilobar subgroups had no significant variations in Problem Solving over time. The temporal subgroup had a significant increase of 1.23 scaled score points between the 12 and the 24 months post-surgical evaluation, $t(177) = -2.19$, $p = .030$. The parietal subgroup had a large increase of 4.96 scaled score points between before surgery and 24 months afterwards, $t(181) = -2.81$, $p = .006$. However, between 24 months and 60 months after surgery, the parietal subgroup lost 5.09 scaled score points, $t(171) = 2.74$, $p = .007$, rendering the 5 year outcome at equal level with the presurgical state of Problem Solving abilities, $t(180) = 0.09$, $p = .93$. The insular subgroup had a significant decrease of 6.00 scaled score points between the evaluation before surgery and 24 months after surgery, $t(167) = 2.14$, $p = .034$.

3.3.2.6. IV Age at Onset: A significant effect of age at onset was shown, $F(1, 139) = 6.33$, $p = .013$. The effects of time and of the interaction time x age at onset were not significant.

Table 63: F-Tests for fixed effects Time, age at onset and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.86	4	200	.49
age_onset	6.33	1	139	**.013**
Time * age_onset	0.18	4	204	.95

Because age at onset is a continuous variable no estimated marginal means can be calculated for it, instead the regression coefficient is interpreted:

Table 64 : Regression Coefficient `age at onset´ for the 5 evaluation times in Problem Solving

Time	*β*	*p*
presurgical IQ = baseline	0.13	.09
6 months	0.17	
12 months	0.18	
24 months	0.16	
60 months	0.23	

To calculate the regression coefficient, the baseline reference category is, as before, the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is 0.13, which is not significant, $t = 1.70$, $p = .09$. So, at the presurgical evaluation, with every year a patient is older at onset of epilepsy, its Problem Solving ability is 0.13 scaled score points higher. The influence of the age at onset of epilepsy on Problem Solving varies across evaluation times: At the 6 months postsurgical evaluation, the Problem Solving ability is 0.17 scaled score points higher for every year a patient is older at onset. At 12 months after surgery the Problem Solving ability is 0.18 scaled score points higher with every year, at 24 months it's 0.16 scaled score points more per year older at the start of epilepsy, and at 60 months after surgery it's 0.23 scaled score points increase per year older at onset.

3.3.2.7. IV Duration of Epilepsy (in Years). A significant effect of duration of epilepsy was revealed, $F(1, 121) = 14.38$, $p < .001$. Neither time nor the interaction Time x duration of epilepsy reached significance, meaning duration of epilepsy before surgery influences the patients Problem Solving abilities independently passing time after surgery. The F-Tests for the main and interaction effects are reported in the following table:

Tableau 65 : F-tests for fixed effects Time, duration of epilepsy and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.36	4	202	.25
Duration of epilepsy (in years)	14.38	1	121	**<.001**
Time *duration of epilepsy	0.99	4	204	.41

As before, because duration of epilepsy is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Tableau 66: Regression coefficient ′duration of epilepsy′ for Problem Solving for the 5 evaluation times

Time	*β*	*p*
presurgical IQ = baseline	-0.16	**.032**
6 months	-0.11	
12 months	-0.07	
24 months	-0.16	
60 months	-0.11	

Again, as in the independent variable 'age at onset of epilepsy', to calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is -0.16, which is significant, t = -2.16, p = .032. This means that at the presurgical evaluation, with every year a patient has been having epilepsy, its problem-solving ability is 0.16 scaled score points lower. The influence of the duration of the illness varies non-significantly across evaluation times: At the 6 months postsurgical evaluation, the problem-solving ability is 0.26 scaled score points lower for every year a patient has been having epilepsy. At 12 months after surgery, Problem Solving is 0.22 scaled score points lower with every year, at 24 months it's 0.32 scaled score points less per year of epilepsy, and at 60 months after surgery it's 0.26 scaled score points decrease per year of epilepsy duration.

3.3.2.8. IV Seizure Outcome. There was no significant effect of time, of the seizure outcome (categories Engel 1a, Engel >1a) or of its interaction. The F-Tests for the main and interaction effects are reported in the following table:

Table 67 : F-tests for fixed effects Time, Seizure outcome (in Engel categories) and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.23	3	200	.30
Engel	0.24	1	252	.62
Time * Engel	0.70	3	202	.56

Again, since the seizure outcome only has 2 features, no overall F-Test was reported, because it is the same as the F-tests for main effects. The estimated marginal means are presented in the Appendix 5. Pairwise comparisons were performed to analyze the evolution of the problem-solving abilities over time, in regard of the of the patients (Appendix 5). Statistically, there were no significant differences between the two patient groups across

evaluation times, whether they still had epileptic seizures after surgery (group '>1a') or not (group '1a').

Other pairwise comparisons, comparing the performance at the 5 evaluation times for each seizure outcome group separately, were conducted (Appendix 5). When comparing the 5 evaluation times in consecutive order, no significant differences could be observed, neither for the seizure free (1a), nor for the group of patients which still had seizures (>1a). A tendency towards significance could be noted for the seizure free group 1a from 6 to 12 months after surgery with a decreasing performance which stabilized in the following postsurgical evaluations. The analysis of the group which was not seizure free also showed a tendency towards significance between 24 and 60 months after surgery, again with decreasing performances in Problem Solving.

3.3.2.9. IV Antiseizure Drug (ASM) Load. There were no significant effects of time, of ASM load or of its interaction. Time x ASM load. The F-Tests for the main and interaction effects are reported in the following table:

Table 68 : F-tests for fixed effects Time, antiseizure drug load (ASM load) and their interaction in Problem Solving

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.32	4	202	.26
ASM load	0.63	2	250	.53
Time x ASM load	0.47	7	205	.86

The overall F- test showed no significant differences between the different ASM load groups at any evaluation time.

Table 69: Overall F-Test results of antiseizure drug load for every evaluation time in Problem Solving

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.41	2	234	.67
6 mo	0.35	1	226	.55
12 mo	0.56	2	223	.57
24 mo	0.75	2	221	.47
60 mo	0.13	2	214	.88

Note. pre = presurgical evaluation, mo = months post-surgery

The estimated marginal means are presented in the Appendix 5. In order to detect significant differences between features of ASM load for each testing time, pairwise

comparisons were conducted. As expected, no significant differences could be noted (Appendix 5). Other pairwise comparisons, comparing the performance at the different evaluation times for each ASM group separately, were not conducted, since these did not make sense: it was expected for most patients to change ASM groups with passing time, when ASM were weaned off after a seizure free period following surgery.

3.3.3. Multivariate analysis of Fluency

The cumulative measure 'phonological Fluency' was used as a dependent variable to evaluate the executive function 'Fluency'. Again, time as well as the same set of possible predictors were used as independent variables. The measure 'Fluency' is indicated in standardized z-scores (mean = 0, standard deviation = 1). 245 values of 89 patients could be included into the following models.

3.3.3.1. IV Presurgical IQ. There was a significant main effect of time, $F(4, 184) = 2.43$, $p = .05$. There was a significant main effect of presurgical IQ, $F(1,91) = 27.04$, $p = <.001$, as well as a significant effect of the interaction time x presurgical IQ on Fluency capacities, $F(4, 182) = 3.24$, $p = .01$. The overall F-test result is significant, $F(4, 176) = 3.62$, $p = .01$. Because presurgical IQ is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 70: Regression coefficient ´presurgical IQ´ in Fluency for the 5 evaluation times

Time	*β*	*p*
presurgical IQ = baseline	1.07	**<.001**
6 months	1.08	
12 months	1.08	
24 months	1.10	
60 months	1.10	

Note. Bold print = significant result.

To calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is 0.01, which is not significant, $t = 1.58$, $p = .12$. This means that at the presurgical evaluation, the higher the IQ, the higher is the performance at the Fluency task. The regression coefficient tells us that with every IQ point difference, the Fluency performance increases by 0.01 points in standardized z-score. The influence of presurgical IQ varies only minimally across evaluation times: At the 6 months

postsurgical evaluation, the Fluency ability is 0.04 points higher in standardized z-score for every additional IQ point. At 12 months after surgery the Fluency ability shows 0.03 points increase in standardized z-score with every additional IQ point, at 24 months it's also 0.03 points increase in standardized z-score per additional IQ point and at 60 months after surgery it's a 0.05 points increase in standardized z-score per additional IQ point.

3.3.3.2. IV Side of Surgery. The main effect of time was significant, $F(4, 170) = 3.60$, $p = .008$, as well as the main effect of side of surgery on which surgery was performed, $F(1, 98) = 4.55$, $p = .036$. However, the interaction Time x side of surgery did not reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 71 : F-Tests for fixed effects time, side of surgery and their interaction in Fluency

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	3.60	4	170	**.008**
side of surgery	4.55	1	93	**.036**
Time x side of surgery	1.26	4	170	.29

The overall F-Test of side of surgery showed significant differences at 24 months post-surgery when comparing the means of the two side of surgery groups. At other evaluation times, no significant differences between the means of the two groups could be found.

Tableau 72 : Overall F-Test results of side of surgery for every evaluation time in Fluency.

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.33	1	170	.57
6 mo	2.67	1	180	.10
12 mo	0.56	1	206	.46
24 mo	5.71	1	199	**.018**
60 mo	2.74	1	235	.10

Note. pre = presurgical evaluation, mo = months posts-surgery

The overall F-Test of time showed a significant difference between the means of the 5 evaluation times in the left side of surgery group, but not in the right.

Table 73: Overall F-Test results of time for every side of surgery in Fluency

side of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
right	1.14	4	173	.34
left	3.66	4	173	**.007**

To examine the significant effect of time, the estimated marginal means are presented in the Appendix 6. Simple contrasts revealed a significant difference between the left and the right side of surgery surgery group at 24 months post-surgery (Appendix 6). Pairwise comparisons were conducted to analyze the evolution of Fluency capacities over time, in regard of the hemisphere on which surgery was performed. For the right hemisphere operated group, a significant change happened between the presurgical evaluation and the 12 months post-surgery evaluation, with a significant increase of 0.42 points in standardized z-score. When comparing the different evaluation times in consecutive order, no significant differences could be observed. For the group, which underwent surgery on the left hemisphere, there were significant changes over time, between the preoperative level and the results at all other evaluation times. A progressive increase of the z-score could be observed (increase of 0.41 points between the presurgical evaluation to the 6 months post-surgery evaluation, up to an increase of 0.95 points between presurgical level and the level at 60 months post-surgery). Here also, when comparing the results at different evaluation times in consecutive order, no significant differences could be observed, implying a slow, but significant growth in Fluency capacities over time.

3.3.3.3. IV Etiology. The effects of time, and interaction Time x etiology did not reach significance, but the main effect of etiology did. The F-Tests for the main and interaction effects are reported in the following table:

Tableau 74 : F-tests for fixed effects of Time, etiology and their interaction in Fluency

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.26	4	148	.07
etiology	4.09	6	82	**.001**
Time x etiology	1.03	19	148	.43

At the 6, 12 and 24 months post-surgery evaluations, there were significant differences between the etiology groups, shown in the overall F-tests. Also again, only the tumor group showed significant differences when comparing the means of all the testing times for each etiology feature in the overall F-tests of time.

Table 75: Overall F-Test results of etiology for every evaluation time in Fluency

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	1.97	6	178	.07
6 mo	3.62	5	197	**.004**
12 mo	3.46	5	200	**.005**
24 mo	2.40	5	214	**.038**
60 mo	2.00	4	215	.10

Note. Time = timing of perisurgical evaluation, pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Table 76: Overall F-test results of time for every etiology type in Planning

etiology	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
MCD	2.35	4	168	.06
tumor	3.19	4	155	**.015**
dual pathology	1.22	4	163	.30
vascular malformation	0.80	3	137	.49
gliosis	0.01	3	144	.99
mesial temporal sclerosis	1.42	4	140	.23
other	1.12	1	135	.29

Note. Bold print = significant result, MCD = malformation of cortical development

To further analyze these findings, the marginal means are presented in the Appendix 6. Deviation contrasts were conducted to analyze the Fluency capacities for all etiology groups at the 5 testing times. Before surgery, only the gliosis group deviated significantly by 0.86 point in z-score above the mean of the surgery cohort, $t(165) = 2.01$, $p = .046$. 6 months after surgery, the MCD group was 0.53 points in z-score significantly below the mean of the cohort, and the vascular malformation group was 1.41 points in z-score significantly below the mean, $t(170) = -2.13$, $p = .035$ and , $t(139) = -2.25$, $p = .026$. At 12 month post-surgery, the tumor group was 0.72 points in z-score above the mean of the cohort, $t(185) = 2.44$, $p = .015$. At 24 months post-surgery, the tumor group was again significantly above the mean of the cohort by 0.73 points in z-score, $t(189) = 2.46$, $p = .015$. At 60 months, the dual pathology group showed significantly lower Fluency performance than the mean of the cohort, with 1.22 points in z-score, less, $t(209) = 2.36$, $p = .019$.

Table 77: Deviation contrasts in Fluency between the mean of the cohort and the etiology groups for every evaluation time in points in z-score.

Time	Etiology deviation Contrasts	Mean difference	*SE*	*t*	*df*	*p*
pre	MCD - Mean	-0.38	0.27	-1.41	151	.16
	tumor - Mean	0.27	0.30	.93	152	.36
	dual pathology - Mean	-0.12	0.34	-.37	163	.71
	vascular malformation - Mean	-1.11	0.66	-1.70	138	.09
	gliosis - Mean	0.86	0.43	2.01	165	**.046**
	mesial temporal sclerosis - Mean	0.32	0.45	.71	139	.48
	other - Mean	0.17	0.91	.18	138	.86
6 mo	MCD - Mean	-0.53	0.25	-2.13	170	**.035**
	tumor - Mean	0.46	0.27	1.71	161	.09
	dual pathology - Mean	0.18	0.31	.59	169	.56
	vascular malformation - Mean	-1.41	0.63	-2.25	139	**.026**
	gliosis - Mean	0.64	0.38	1.66	155	.10
	mesial temporal sclerosis - Mean	0.67	0.48	1.38	185	.17
12 mo	MCD - Mean	-0.45	0.26	-1.73	182	.09
	tumor - Mean	0.72	0.29	2.44	185	**.015**
	dual pathology - Mean	-0.62	0.32	-1.96	176	.052
	vascular malformation - Mean	-0.64	0.63	-1.03	139	.31
	gliosis - Mean	0.47	0.40	1.16	169	.25
	mesial temporal sclerosis - Mean	0.54	0.42	1.27	141	.21
24 mo	MCD - Mean	-0.12	0.27	-.46	193	.65
	tumor - Mean	0.73	0.30	2.46	189	**.015**
	dual pathology - Mean	-0.35	0.34	-1.01	192	.32
	vascular malformation - Mean	-0.97	0.78	-1.25	202	.22
	gliosis - Mean	0.74	0.41	1.80	177	.07
	mesial temporal sclerosis - Mean	-0.04	0.43	-.08	149	.94
60 mo	MCD - Mean	-0.31	0.39	-.78	203	.43
	tumor - Mean	0.60	0.46	1.30	214	.20
	dual pathology - Mean	-1.22	0.52	-2.36	209	**.019**
	mesial temporal sclerosis - Mean	0.52	0.72	0.72	212	.47
	other - Mean	0.42	0.86	0.48	145	.63

Note. pre = presurgical evaluation, mo = months post-surgery, MCD = malformation of cortical development

Pairwise comparisons allowed to analyze in an explorative manner the development of Fluency capacities for the different etiology groups across time (Appendix 6). In the MCD group, a significant increase of 0.87 points in z-score could be observed between the presurgical and the 60 months post-surgical evaluation, $t(212) = -2.56$, $p = .011$. The tumor group differed

significantly across testing times: There was a significant increase of 0.86 points in z-score between the presurgical and the 12 months post-surgical evaluation, $t(143) = -3.05$, $p = .003$, as well as a significant increase of 0.63 points in z-score between the presurgical and the 24 months post-surgical evaluation, $t(145) = -2.33$, $p = .021$. There was also a significant increase of 1.12 points in z-score between the presurgical and the 60 months post-surgical evaluation, $t(186) = -2.41$, $p = .017$. However, the increase in consecutive order from presurgical evaluation to the 6 months post-surgical evaluation, then to 12 months, 24 months and 60 months after surgery was not significant.

3.3.3.4. IV Surgery Type. In the F-tests for fixed effects, the effects of surgery type and interaction Time x surgery type did not reach significance. However, the F-test for the main effect of time was significant. The F-Tests for the main and interaction effects are reported in the following table:

Table 78 : F-Tests for fixed effects time, surgery type and their interaction in Fluency

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	3.46	4	150	**.010**
Surgery type	0.92	5	79	.48
Time x surgery type	1.29	19	151	.20

The overall F-tests of surgery type were all non-significant (Appendix 6). The overall F-test of time revealed significant differences between evaluation times in Fluency in the lesionectomy group, $F(4, 161) = 2.87$, $p = .025$, as well as in the temporal tailored resection + AHE group, $F(3, 152) = 4.05$, $p = .008$.

To analyze the Fluency abilities for all surgery groups at the 5 testing times, deviation contrasts were conducted (Appendix 6). The 6 features of surgery type were compared with the mean of all features combined, for each of the testing times. At the presurgical evaluation, as well as at the 12- and 60-months appointments, no significant differences could be observed between the surgery groups. At the 6 months post-surgery evaluation, the lesionectomy group scored 0.76 points in z-score significantly lower than the mean of the cohort. At 24 months after surgery, only the temporal tailored resection + AHE group was 0.94 points in z-score lower than the mean of the whole surgery group, which was significant.

For each surgery group, pairwise comparisons were conducted, to look for significant differences of Fluency within each group, across evaluation times (Appendix 6). The lesionectomy group differed significantly with an increase of 0.64 points in z-score between the pre surgical and the 12 month post-surgical evaluation, $t(144) = -2.09$, $p = .038$, as well as

with an increase of also 0.64 points in z-score between the pre surgical and the 24 months post-surgical evaluation, $t(150) = -2.32$, $p = .022$, as well as an increase of 1.3 points in z-score between presurgical and 60 months post-surgical evaluation. The standard temporal resection ± AHE group did have significant increases of 0.78 and 1.18 points in z-score, respectively between the presurgical evaluation and the 24 months postsurgical evaluation, $t(147) = -2.16$, $p = .032$, and between the presurgical and the 60 months postsurgical evaluation, $t(191) = -2.10$, $p = .037$.

For all of these significant changes between presurgical and postsurgical evaluations, the increase in consecutive order from presurgical evaluation to the 6 months post-surgical evaluation, then to 12 months, 24 months and 60 months after surgery was not significant, except for the temporal tailored resection + AHE group: Between the presurgical and the 6months postsurgical evaluation, the Fluency score increased significantly by 1.34 points in z-score, $t(160) = -2.69$, $p = .008$. Between 12 and 24 months after surgery, the Fluency score increased by 0.92 points in z-score, which is also significant, $t(140) = -2.06$, $p = .042$. In this group, there was no evaluation at 60 months after surgery. All the details of these pairwise comparisons can be looked up in Appendix 6.

3.3.3.5. IV Localization. Neither the effect of localization of surgery nor the effect of time and the interaction effect time x localization were significant. The F-Tests for the main and interaction effects are reported in the following table:

Table 80: F-Tests for fixed effects time, surgery type and their interaction in Fluency

Source	F	$df_{Nom.}$	$df_{Denom.}$	p
Time	0.99	4	159	.42
localization	1.62	5	86	.16
Time * localization	0.65	16	155	.84

However, the overall F-test results of localization showed significant differences between the Fluency capacities of the localization groups at 6 months after surgery, $F(4,204) = 3.58$, $p = .008$ (Appendix 6). The overall F-test results of time showed significant differences between evaluation times within the frontal group and within the temporal group, as shown in the table below.

Table 81: Overall F-Test Results of time for every localization group in Fluency

localization	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
frontal	2.55	4	163	**.041**
temporal	2.58	4	155	**.039**
parietal	0.21	4	176	.93
occipital	0.02	3	139	.99
insular	0.03	1	136	.86
multilobar	0.92	4	171	.49

Estimated marginal means are presented in a table in the appendix (Appendix 6). In order to analyze the Fluency capacity, deviation contrasts were conducted for all localization groups at the 5 testing times. Two deviation contrast were significant: The frontal localization group had significantly lower performance in Fluency, before and 6 months after surgery: Before surgery, its mean was 0.60 points in z-score under the mean of the whole surgery cohort, $t(155) = -2.21$, $p = .029$. Right after surgery, its mean was 0.60 points in z-score under the mean of the whole surgery cohort, $t(164) = -3.46$, $p = .001$.

As before, pairwise comparisons were conducted to analyze the development of Fluency capacities for the different localization groups across the postoperative timespan (Appendix 6). The detailed results can be seen in figure below. The parietal, occipital, insular und multilobar subgroups had no significant variation in Fluency abilities over time. The frontal subgroup had a significant increase of 0.95 points in z-score between the presurgical and the 60 months post-surgical evaluation, $t(213) = -2.29$, $p = .023$. The increase from presurgical evaluation to the 6 months post-surgical evaluation, then to 12 months and 24 months after surgery were not significant. The temporal group showed a significant increase of 0.45 points in z-score 6 months after surgery, $t(148) = -2.20$, $p = .029$. When compared to the Fluency level before surgery, the temporal group also showed a significant increase of 0.55 points in z-score at 12 months after surgery, $t(145) = -2.70$, $p = .008$. However, when comparing the scores 6 months and 12 months post-surgery, no significant difference could be found. Also, when comparing the Fluency capacities before surgery and 60 months after surgery, a significant increase of 0.75 points in z-score was found, $t(175) = -2.01$, $p = .046$. Again, no significant increase could be observed when checking chronologically from 12 to 24 to 60 months after surgery. This means that, the significant increase from before surgery to 60 months after surgery was very slow yet significant.

3.3.3.6. IV Age at Onset. The effect of age at onset was significant, $F(1, 177) = 0.313$, $p = .002$. The effect of time and the interaction effect time x age at onset did not reach

significance, $F(4, 185) = 0.87$ $p = .49$ and $F(4, 177) = 0.31$ $p = .87$. Again, because age at onset is a continuous variable no estimated marginal means can be calculated for it, instead the regression coefficient is interpreted:

Table 82: Regression coefficient `age at onset´for the 5 evaluation times in Fluency

time	*β*	*p*
Presurgical evaluation = baseline	0.06	**.021**
6months	0.04	
12 months	0.08	
24 months	0.07	
60 months	0.08	

As before, to calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is 0.06, which is significant, $t = 2.33$ $p = .021$. This means that at the presurgical evaluation, with every year a patient is older at onset of epilepsy, its Planning ability is 0.06 points in z-score higher. The influence of the age at onset of epilepsy varies a little across evaluation times: At the 6 months postsurgical evaluation, the Fluency ability is 0.04 points in z-score lower for every year a patient is older at onset. At 12 months after surgery the Fluency ability is on rise again, with 0.08 points in z-score higher with every year a patient is older at onset, at 24 months it's 0.07 points in z-score more per year older at the start of epilepsy, and at 60 months after surgery it's 0.08 points in z-score increase per year older at onset.

3.3.3.7. IV Duration of Epilepsy (in Years). The effect of duration of epilepsy was significant, $F(1, 119) = 8.44$, $p = .004$. Neither the effect of time nor the interaction effect Time x duration of epilepsy reached significance, meaning the duration of epilepsy at surgery influences the patients Fluency abilities independently of passing time. The F-Tests for the main and interaction effects are reported in the following table:

Table 83: F-tests for fixed effects Time, Duration of epilepsy and their interaction in Fluency

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.57	4	174	.19
Duration of epilepsy (in years)	8.44	1	119	**.004**
Time x duration of epilepsy	0.14	4	178	.97

Note. bold print = significant result

Because duration of epilepsy is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 84: Regression coefficient `duration of epilepsy´ for the 5 evaluation times in Fluency

time	*β*	*p*
Presurgical evaluation = baseline	-0.06	**.034**
6months	-0.07	
12 months	-0.07	
24 months	-0.08	
60 months	-0.08	

As previously, in order to calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At baseline, the coefficient is -.058, which is significant, t = -2.13, p = .034. This means that at the presurgical evaluation, with every year a patient has been having epilepsy, its Fluency ability is 0.06 points in z-score lower. The influence of the duration of the illness varies very slightly across evaluation times: At the 6 months postsurgical evaluation, the fluence ability is 0.07 points in z-score lower for every year a patient has been having epilepsy. At 12 months after surgery Fluency is also just 0.07 points in z-score lower with every year, at 24 months it's 0.08 points in z-score less per year of epilepsy, and at 60 months after surgery it's also 0.08 points in z-score decrease per year of epilepsy duration.

3.3.3.8. IV Seizure Outcome. There was no significant effect of time, of the Seizure outcome (categories Engel 1a, Engel >1a) or of its interaction. The F-Tests for the main and interaction effects are reported in the following table:

Table 85: F-Tests for fixed effects Time, Seizure outcome (in Engel categories) and their interaction in Fluency

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.19	3	180	.314
Engel	3.46	1	231	.06
Time * Engel	0.20	3	182	.90

Since the seizure outcome variable only has 2 features, no overall F-Test was reported, because it is the same as the F-tests for main effects. The estimated marginal means are presented in the Appendix 6. Pairwise comparisons were conducted to analyze the evolution of the Fluency abilities over time, in regard of the Seizure outcome of the patients. There were no significant differences in Fluency abilities between the two patient groups across evaluation

times, whether they still had epileptic seizures after surgery (group '>1a') or not (group '1a'). There seems to be a trend towards steadily growing Fluency capacities across time in both groups. The large standard errors and the small cohort size can possibly account for non-significance in the statistical analyses.

Table 86: Pairwise comparisons between both seizure outcome groups (in Engel categories) for each evaluation time in Fluency

Time	Engel Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
6 mo	1a - > 1a	-0.40	0.26	-1.53	193	.13
12 mo	1a - > 1a	-0.37	0.27	-1.37	197	.17
24 mo	1a - > 1a	-0.17	0.25	-0.70	187	.49
60 mo	1a - > 1a	-0.37	0.44	-0.85	230	.39

Note. mo = months post-surgery

Other pairwise comparisons, comparing the performance at the different evaluation times for each seizure outcome group separately, were conducted. When comparing the different evaluation times in consecutive order, no significant differences could be observed, neither for the the seizure free (1a), nor for the group of patients which still had seizures (>1a).

Tableau 87 : Pairwise comparisons between consecutive evaluation times for each seizure outcome group in Fluency.

Seizure outcome	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p*
1a	6 mo - 12 mo	-0.18	0.17	-1.05	157	.30
	12 mo - 24 mo	0.09	0.18	0.49	156	.63
	24 mo - 60 mo	-0.29	0.32	-0.92	219	.36
>1a	6 mo - 12 mo	-0.14	0.29	-0.49	170	.62
	12 mo - 24 mo	0.28	0.27	1.03	169	.30
	24 mo - 60 mo	-0.49	0.36	-1.36	208	.18

Note. mo = months post-surgery

3.3.3.9. IV Antiseizure Drug (ASM) Load. There were no significant effects of time, ASM load or of its interaction Time x ASM load. The F-Tests for the main and interaction effects are reported in the following table:

Table 88 : F-Tests for fixed effects Time, antiseizure drug load (ASM) and their interaction in Fluency

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.08	4	178	.09
ASM load	0.78	2	218	.46
Time x ASM load	0.18	6	182	.98

The overall F- tests showed no significant differences between the different ASM load groups at the 5 evaluation times.

Table 89 : Overall F-Test results of antiseizure drug load for every evaluation time in Fluency

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.16	1	183	.69
6 mo	0.01	1	189	.98
12 mo	0.20	2	181	.82
24 mo	0.42	2	185	.66
60 mo	0.63	2	223	.53

Note. mo = months post-surgery

The estimated marginal means are presented in the Appendix 6. To observe the evolution of the Fluency abilities over time, pairwise comparisons were conducted. However, all comparisons between ASM groups did not lead to significant differences, at any evaluation time. Pairwise comparisons can be found in Appendix 6. Other pairwise comparisons, comparing the performance at the different evaluation times for each ASM group separately, were not conducted, since these did not make sense: it was expected for most patients to change ASM groups with passing time, when ASM were weaned off after a seizure free period following surgery.

3.3.4. Multivariate Analysis of Working Memory

For the multivariate multilevel analyses, the cumulative measure ‘digit span’ was used as a dependent variable to evaluate the executive function ‘Working Memory’. So, the dependent variable will be referred to as ‘Working Memory’. Same as for the other dependent variables, time as well as the same set of possible predictors were used as independent variables. The measure ‘Working Memory’ is indicated in scaled scores as used in the Wechsler Intelligence tests (mean = 10, standard deviation = 3). 322 values of 109 patients could be included into the following models.

3.3.4.1. IV Presurgical IQ. No significant main effect of time could be found, $F(9, 198) = 5.75$, $p = .79$. However, there was a significant main effect of presurgical IQ, $F(1,129) = 32.12$, $p = <.001$. The interaction time x presurgical IQ on Working Memory capacities was not significant, $F(4, 224) = 0.20$, $p = .94$. Because presurgical IQ is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 90: Regression coefficient `presurgical IQ´ for the 5 evaluation times in Working Memory

time	*β*	*p*
Presurgical evaluation = baseline	0.11	**<.001**
6months	0.10	
12 months	0.09	
24 months	0.09	
60 months	0.10	

To calculate the coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is 0.11, which is significant, $t= 5.65$, $p = <.001$. This means that at the presurgical evaluation, the higher the IQ, the higher is the Working Memory performance. The regression coefficient signifies that with every IQ point difference, the Working Memory performance increases by 0.11 scaled score points. The influence of presurgical IQ does barely change across evaluation times: At the 6 months postsurgical evaluation, the Working Memory ability is 0.10 scaled score points higher for every additional IQ point. At 12 months after surgery the Working Memory ability is 0.09 scaled score points higher with every additional IQ point, at 24 months it's also 0.09 scaled score points more per additional IQ point and at 60 months after surgery it's 0.10 scaled score points increase per additional IQ point.

3.3.4.2. IV Side of Surgery. The main effect of time was significant, $F(4, 220) = 2.91$, $p = .023$, as well as the main effect of side of surgery on which surgery was performed, $F(1, 133) = 6.72$, $p = .011$. However, the interaction Time x side of surgery did not reach significance, $F(4, 220) = 0.50$, $p = .74$. The F-Tests for the main and interaction effects are reported in the following table:

Table 91 : F-Tests for fixed effects time, side of surgery and their interaction in Working Memory

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.91	4	220	**.023**
side of surgery	6.72	1	133	**.011**
Time x side of surgery	0.50	4	220	.74

The overall F-Test of side of surgery showed significant differences at 12 and at 24 months post-surgery when comparing the means of the two side of surgery groups. At other evaluation times, no significant differences between the means of the two groups could be found.

Table 92 : Overall test results of side of surgery for every evaluation time in Working Memory

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	3.30	1	173	.07
6 mo	2.60	1	235	.11
12 mo	7.61	1	201	**.006**
24 mo	4.21	1	235	**.041**
60 mo	2.40	1	296	.12

Note. pre = presurgical evaluation, mo = months post-surgery

As for other dependent variables, the overall F-Test of time showed a significant difference between the means of the 5 evaluation times in the left hemisphere group, but not in the right.

Table 93: Overall test results of time for every side of surgery in Working Memory

side of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
right	0.80	4	221	.53
left	2.66	4	219	**.034**

To examine the significant effect of time, the estimated marginal means are presented in the Appendix 7. Simple contrasts revealed a significant difference between the left and the right hemisphere surgery group at 12 and at 24 months post-surgery. The group with surgery on the left hemisphere had significantly higher Working Memory performances at both evaluations, 1.58 scaled scores higher at 12 months and 1.26 scaled scores higher at 24 months past surgery.

Table 94: Simple contrasts in scaled score points between both side of surgery subgroups for each evaluation time in Working Memory.

Time	side of surgery Simple Contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	right - left	-0.98	0.54	-1.82	173	.07
6 mo	right - left	-0.99	0.61	-1.61	235	.11
12 mo	right - left	-1.58	0.57	-2.76	201	**.006**
24 mo	right - left	-1.26	0.61	-2.05	235	**.041**
60 mo	right - left	-1.71	1.11	-1.56	296	.12

Note. pre = presurgical evaluation, mo = months post-surgery

In order to analyze the evolution of Working Memory capacities over time, in regard of the hemisphere on which surgery was performed, pairwise comparisons were conducted. For the right hemisphere operated group, no significant changes happened between evaluations. For the group, which underwent surgery on the left hemisphere, there were significant changes over time, between the preoperative level and the results at 12 and 24 months post-surgery, as well as between the 6 and the 12 months post-surgery evaluations. A progressive increase of scaled scores could be observed, 0.80 scaled score points between the presurgical evaluation to the 12 months post-surgery evaluation, and 0.9 scaled score points between presurgical workup and the 24 months postsurgical evaluation. When comparing the 6 and 12 months postsurgical evaluations, a significant increase of 0.80 scaled score points could be observed.

Table 95 : Pairwise comparisons of Working memory scores in scaled score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each side of surgery.

side of surgery	Time Pairwise Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
	pre - 6 mo	0.01	0.38	0.02	221	.98
	pre - 12 mo	-0.20	0.35	-0.58	218	.57
	pre - 24 mo	-0.62	0.38	-1.64	221	.10
right	pre - 60 mo	-0.41	0.84	-0.49	226	.63
	6 mo - 12 mo	-0.21	0.40	-0.51	216	.61
	12 mo - 24 mo	-0.42	0.40	-1.06	216	.29
	24 mo - 60 mo	0.21	0.87	0.24	227	.81
	pre - 6 mo	0.002	0.39	0.01	214	.99
	pre - 12 mo	-0.80	0.35	-2.25	212	**.026**
	pre - 24 mo	-0.90	0.40	-2.27	218	**.024**
left	pre - 60 mo	-1.16	0.66	-1.73	234	.09
	6 mo - 12 mo	-0.80	0.39	-2.03	213	**.044**
	12 mo - 24 mo	-0.10	0.40	-0.26	213	.80
	24 mo - 60 mo	-0.25	0.68	-0.37	231	.71

Note. pre = presurgical evaluation, mo = months post-surgery

3.3.4.3. IV Etiology. The main effect of etiology reached significance, but the effects of time, and interaction Time x etiology did not. The F-Tests for the main and interaction effects are reported in the following table:

Table 96 : F-Tests for fixed effects Time, etiology and their interaction in Working Memory

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.59	4	198	.67
etiology	2.21	6	112	**.047**
Time x etiology	0.63	19	200	.88

At the 12 months post-surgery evaluation, there was a significant difference between the etiology groups, shown in the overall F-tests, but not at other evaluation times. The overall F-Tests of time showed no significant differences within an etiology group, when comparing the means of all the testing times.

Table 97 : Overall test results of etiology for every evaluation time in Working Memory

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	1.62	6	190	.15
6 mo	1.73	5	266	.13
12 mo	2.42	5	212	**.037**
24 mo	1.56	5	263	.17
60 mo	1.26	4	292	.29

Note. pre = presurgical evalution, mo = months post-surgery, bold print = significant result

Table 98 : Overall test results of time for every etiology subgroup in Working Memory

etiology	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
MCD	1.96	4	206	0.10
tumor	2.13	4	205	0.08
dual pathology	0.08	4	201	0.99
vascular malformation	0.42	3	193	0.74
gliosis	0.11	3	205	0.96
mesial temporal sclerosis	1.24	4	196	0.29
other	0.01	1	191	1.00

Note. MCD = malformation of cortical development

To further analyze these findings, the marginal means are presented in the Appendix 7. To analyze the Working Memory abilities for all etiology groups at the 5 testing times, deviation contrasts were conducted (Appendix 7). Before the surgical intervention, only the MCD group deviated significantly by 1.67 scaled score points below the mean of the surgery cohort, $t(160) = 2.57$, $p = .011$. 6 months after surgery, the MCD group was 1.50 scaled score points significantly below the mean of the cohort, $t(176) = -2.60$, $p = .010$. At 12 month post-surgery, the MCD group was 1.51 scaled score points below the mean of the cohort, $t(176) = -2.60$, $p = .010$. At 24 months post-surgery, the mesial temporal sclerosis group was significantly above the mean of the cohort by 2.51 scaled score points, $t(256) = 0.22$, $p = .027$. At 60 months, no group differed significantly from the mean of the cohort.

Pairwise comparisons were performed in order to analyze the Working Memory abilities for the different etiology groups across the 5 testing times (Appendix 7). In the MCD group, a significant increase of 1.03 scaled score points could be observed between the presurgical and the 24 months post-surgical evaluation, $t(202) = -2.29$, $p = .023$. There was a significant increase in the tumor group of 1.26 scaled score points between the presurgical and the 12 months post-surgical evaluation, $t(200) = -2.58$, $p = .015$. All other testing times did not differ significantly from one another, no significant differences were noted across evaluation times in other etiology groups.

3.3.4.4. IV Surgery Type. In the F-tests for fixed effects, the effects of surgery type, time and interaction of time x surgery type did not reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 99 : F-Tests for fixed effects Time, surgery type and their interaction in Working Memory

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.18	4	200	**.07**
Surgery type	2.14	5	112	.07
Time x surgery type	0.41	19	202	.99

The overall F-tests of surgery type were all not significant. The overall F-test of time also revealed no significant differences between evaluations in the different surgery groups (Appendix 7). The estimated marginal means and standard errors for time can be looked up in Appendix 7. Deviation contrasts were conducted to analyze the Working Memory abilities for all surgery groups at the 5 evaluation times (Appendix 7). At the presurgical evaluation, as well as at the 12 and 60 months post-surgery testings, no significant differences could be observed between the surgery groups. At the 6 months post-surgery evaluation, the intralobar tailored resection group scored 1.62 scaled score points significantly lower than the mean of the cohort. At 24 months after surgery, the intralobar tailored resection group scored 1.24 scaled score points lower than the mean, and the AHE group scored significantly 3.37 scaled score point above the mean of the cohort.

As before in other independent variables, pairwise comparisons were conducted for each surgery group, to look for significant differences of Working Memory within each group, across evaluation times. Only the intralobar tailored resection group differed significantly with an increase of 1.14 scaled score points between the 6 and the 12 months post-surgical evaluation, $t(197) = -2.24$, $p = .026$. All other comparisons were not significant (Appendix 7).

3.3.4.5. IV Localization. Neither the effect of localization of surgery nor the effect of time and the interaction effect time x localization were significant. The F-Tests for the main and interaction effects are reported in the following table:

Table 100 : F-Tests for fixed effects Time, localization and their interaction in Working Memory

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.71	4	202	.15
localization	1.52	5	115	.19
Time * localization	0.74	16	203	.75

The overall F-test results of localization showed no significant differences between the Working Memory capacities of the localization groups (Appendix 7). The overall F-test results of time showed significant differences between evaluation times within the frontal group, as shown in the table below.

Table 101: Overall test results of time for every localization group in Working Memory

localization	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
frontal	2.80	4	210	**.027**
temporal	0.77	4	206	.55
parietal	0.74	4	204	.57
occipital	0.54	3	197	.66
insular	3.09	1	193	.08
multilobar	0.58	4	204	.68

Note. Bold print = significant result

Estimated marginal means are presented in a table in the Appendix 7. At 60 months post-surgery, there was no data available for the occipital group. Deviation contrasts were conducted for all localization groups at the 5 testing times to analyze the Working Memory abilities (Appendix 7). Only one deviation contrast was significant: The frontal localization group had significantly lower performance in Working Memory, 6 months after surgery: Before surgery, its mean was 0.58 scaled score points under the mean of the whole surgery cohort but 6 months after surgery it went up to 1.27 scaled score points difference with the mean of the whole group, $t(208) = -2.03$, $p = .044$. At 60 months after surgery, the frontal group was almost at the group mean level, with a difference of only 0.08 scaled score points below, $t(294) = -0.1$, $p = .93$.

Pairwise comparisons were performed to analyze the development of Working Memory capacities for the different localization groups across the postoperative timespan (Appendix 7). The temporal, parietal, occipital, insular und multilobar subgroups had no significant variation in Working Memory abilities over time. The insular group had data available only before and 12 months after surgery, the occipital group only up to 24 months after surgery. Only one pairwise comparison reached significance, the frontal group gained a significant 1.13 scaled score points between the 6 and the 12 months postsurgical evaluation.

3.3.4.6. IV Age at Onset. The effect of age at onset was significant, $F(1, 142) = 12.32$, $p = .001$. The effect of time and the interaction effect time x age at onset did not reach

significance, $F(4, 219) = 0.71$, $p = .59$ and $F(4, 224) = 0.48$, $p = .75$. The overall F-test result for time is significant, $F(4, 222) = 2.98$, $p = .023$. As age at onset is a continuous variable, no estimated marginal means can be calculated for it, instead the regression coefficient is interpreted:

Tablea 102 : Regression coefficient ´age at onset´ in Working Memory for the 5 evaluation times

time	*β*	*p*
Presurgical evaluation = baseline	0.15	**.011**
6months	0.16	
12 months	0.16	
24 months	0.16	
60 months	0.16	

To calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At baseline, the coefficient is 0.15, which is significant, $t = 2.58$, $p = .011$. This means that at the presurgical evaluation, with every year a patient is older at onset of epilepsy, its Working Memory ability is 0.15 scaled score points higher. The influence of the age at onset of epilepsy does almost not vary across evaluation times: At the 6 months postsurgical evaluation, the Working Memory ability is 0.16 scaled score points higher for every year a patient is older at onset. At 12 months after surgery the Working Memory ability is also rising by 0.16 scaled score points with every year a patient is older at onset, at 24 months it's, again, 0.16 scaled score points more per year older at the start of epilepsy, and at 60 months after surgery it's 0.16 scaled score points increase per year older at onset.

3.3.4.7. IV Duration of Epilepsy (in Years). The effect of duration of epilepsy was significant, $F(1, 244) = 5.15$, $p = .024$. Neither the effect of time nor the interaction effect Time x duration of epilepsy reached significance, meaning the duration of epilepsy at surgery influences the patient's Working Memory abilities independently of passing time. The F-Tests for the main and interaction effects are reported in the following table:

Table 103 : F-Tests for fixed effects Time, Duration of epilepsy (in years) and their interaction in Working Memory

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.87	4	227	.48
Duration of epilepsy (in years)	5.15	1	244	**.024**
Time x duration of epilepsy	0.16	4	224	.96

Because duration of epilepsy is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 104 : Regression coefficient ´duration of epilepsy´ for Working Memory for the 5 evaluation times

time	*β*	*p*
Presurgical evaluation = baseline	-0.19	**.003**
6months	-0.14	
12 months	-0.17	
24 months	-0.16	
60 months	-0.18	

To calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. The coefficient at baseline is -0.19, which is significant, t= -3.04, p = .003. This means that at the presurgical evaluation, with every year a patient has been having epilepsy, its Working Memory ability is 0.19 scaled score points lower. The influence of the duration of the illness varies only a little across evaluation times: At the 6 months postsurgical evaluation, the Working Memory ability is 0.14 scaled score points lower for every year a patient has been having epilepsy. At 12 months after surgery Planning is just 0.17 scaled score points lower with every year, at 24 months it's 0.16 scaled score points decrease per year of epilepsy duration. And at 60 months after surgery it's 0.18 scaled score points less per year of having had epilepsy at surgery.

3.3.4.8. IV Seizure Outcome. There was no significant effect of time, of the seizure outcome or of its interaction. The F-Tests for the main and interaction effects are reported in the following table:

Table 105 : F-Tests for fixed effects Time, seizure outcome and their interaction in Working Memory

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.27	3	216	.08
Engel	0.01	1	256	.92
Time x Engel	0.21	3	218	.90

Note. Engel = seizure outcome expressed as Engel classification.

The seizure outcome only has 2 features (Engel 1a, Engel >1a), so no overall F-Test was conducted, because it is the same as the F-tests for main effects. The estimated marginal means are presented in the Appendix 7. Simple contrasts were performed in regard of the Seizure

outcome of patients to analyze the evolution of the Working Memory abilities over time. There were no significant differences in Working Memory between the two patient groups across evaluation times. Despite that there was no significant effect of time on Working Memory ability here, there seems to be a trend towards steadily growing working performances across time in both groups. The large standard errors and the small cohort size can possibly account for non-significance in the statistical analyses.

Tableau 106 : Simple contrasts between seizure outcome groups for each postsurgical evaluation time in Working Memory

Time	Engel outcome comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
6 mo	1a - > 1a	0.15	0.58	0.26	236	.80
12 mo	1a - > 1a	0.33	0.48	0.69	240	.49
24 mo	1a - > 1a	-0.12	0.50	-0.24	236	.81
60 mo	1a - > 1a	-0.21	1.11	-0.19	235	.85

Note. mo = months post-surgery, Engel = seizure outcome expressed in Engel categories

Pairwise comparisons, comparing the performance at the different evaluation times for each seizure outcome group separately, were conducted. When comparing the different evaluation times in consecutive order, no significant differences could be observed, neither for the the seizure free (1a), nor for the group of patients which still had seizures (>1a).

Table 107 : Pairwise comparisons between consecutive evaluation times for each seizure outcome group in Working Memory

Seizure outcome	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
1a	6 mo - 12 mo	-0.58	0.34	-1.70	207	.09
	12 mo - 24 mo	-0.13	0.37	-0.35	208	.73
	24 mo - 60 mo	-0.09	0.86	-0.10	247	.92
>1a	6 mo - 12 mo	-0.40	0.57	-0.69	210	.49
	12 mo - 24 mo	-0.58	0.49	-1.20	208	.23
	24 mo - 60 mo	-0.18	0.81	-0.22	211	.89

Note. mo = months post-surgery, seizure outcome = expressed in Engel categories.

3.3.4.9. IV Antiseizure Drug (ASM) Load. There were no significant effects of time and of its interaction Time x ASM load. The effect of ASM load was significant. The F-Tests for the main and interaction effects are reported in the following table:

Table 108 : F-Tests for fixed effects Time, ASM load and their interaction, in Working Memory

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.34	4	229	.26
ASM load	4.13	2	265	**.017**
Time x ASM load	0.77	7	228	.61

Note. ASM load = antiseizure drug load, bold print = significant result

The overall F- tests showed significant differences between the different ASM load groups at the presurgical evaluation as well as at the 12 months postsurgical evaluation.

Table 109 : Overall Test Results of ASM load for every evaluation time in Working Memory

time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	4.80	2	252	**.009**
6 mo	1.54	1	242	.22
12 mo	3.14	2	235	**.045**
24 mo	1.23	2	231	.29
60 mo	0.43	2	249	.65

Note. pre = presurgical evaluation, mo = months post-surgery, bold print = significant result, ASM load = antiseizure drug load

The estimated marginal means and standard errors of time are presented in the Appendix 7. Pairwise comparisons were conducted to analyze the significant differences that appear to exist between the ASM groups. At presurgical evaluation, there was a significant difference of between the non ASM group and the 1 ASM group, as well as between the non ASM group and the >1 ASM group. There are also significant differences between these groups at 12 months after surgery. 6 months after surgery, there were no patients who didn't take ASM. At the 24 and 60 months after surgery evaluations none of the groups differed significantly from the others.

Other pairwise comparisons, comparing the performance at the different evaluation times for each ASM group separately, were not conducted, since these did not make sense: it was expected for most patients to change ASM groups with passing time, when (some) ASM were weaned off after a long seizure free period following surgery.

Table 110: Pairwise comparisons of Working Memory scores in scaled score points between the antiseizure drug load groups for every evaluation time

Time	ASM Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
	0 - 1	3.01	1.45	2.07	247	**.039**
pre	0 - > 1	3.82	1.43	2.68	248	**.008**
	1 - > 1	0.82	0.45	1.82	256	.07
6 mo	1 - > 1	0.61	0.49	1.24	242	.22
	0 - 1	1.80	0.88	2.05	223	**.041**
12 mo	0 - > 1	2.26	0.91	2.50	228	**.013**
	1 - > 1	0.46	0.46	0.98	248	.33
	0 - 1	0.71	0.58	1.21	229	.23
24 mo	0 - > 1	1.03	0.68	1.52	236	.13
	1 - > 1	0.32	0.59	0.55	230	.59
	0 - 1	-0.78	1.67	-0.47	280	.64
60 mo	0 - > 1	0.29	1.76	0.17	277	.87
	1 - > 1	1.07	1.19	0.90	221	.37

Note. ASM = antiseizure drug load groups, pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation

3.3.5. Mulitvariate Analysis of Inhibition

The evaluation of the executive function Inhibition was based on the cumulative measure ‘D2-KL’ as a dependent variable, which will be referred to as `Inhibition´ throughout this chapter. As for the other dependent variables, time as well as the same set of possible predictors were used as independent variables. ‘Inhibition’ is indicated in standard scores (mean = 100, standard deviation = 15). 126 values of 53 patients could be included into the following models.

3.3.5.1. IV Presurgical IQ. No significant main effect of time could be found, $F(9, 74) = 1.75$, $p = .15$. However, there was a significant main effect of presurgical IQ, $F(1,54) = 7.75$, $p = .01$. The interaction time x presurgical IQ on Inhibition showed a tendency toward significance, $F(4, 82) = 2.20$, $p = .08$. Because presurgical IQ is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 111: Regression coefficient ´presurgical IQ´ for Inhibition for the 5 evaluation times

time	*β*	*p*
Presurgical evaluation = baseline	0.12	.38
6months	0.34	
12 months	0.13	
24 months	0.47	
60 months	0.65	

To calculate the coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At the baseline, the coefficient is 0.12, which is not significant, $t = 0.89$, $p = .38$. This means that at the presurgical evaluation, the higher the IQ, the higher is the performance at the Inhibition task. The regression coefficient tells us that with every IQ point difference, the Inhibition performance increases by 0.12 points in standardized z-score per additional IQ point. At the 6 months postsurgical evaluation, Inhibition performance is 0.34 standard score points higher for every additional IQ point a patient obtains. At 12 months after surgery Inhibition is 0.13 points higher with every additional IQ point, at 24 months it's 0.47 points more per additional IQ point and at 60 months after surgery it's 0.65 points increase per additional IQ point.

3.3.5.2. IV Side of Surgery. Neither the interaction effect time x side of surgery did reach significance, nor the main effects time and side of surgery. The F-Tests for the main and interaction effects are reported in the following table:

Table 112: F-Tests for fixed effects Time, side of surgery and their interaction in Inhibition.

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.54	4	74	.20
Side of surgery	2.53	1	49	.12
Time x side of surgery	0.22	4	74	.93

The overall F-Test of side of surgery showed no significant differences when comparing the means of the two side of surgery groups at all evaluation times.

Table 113: Overall F-Tests results of side of surgery for every evaluation time in Inhibition

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	3.29	1	84	.07
6 mo	1.23	1	94	.27
12 mo	0.74	1	106	.39
24 mo	1.73	1	102	.19
60 mo	1.02	1	113	.32

Note. pre = presurgical evaluation, mo = months post-surgery

As for other dependent variables, the overall F-Test of time showed no significant differences between the means of the 5 evaluation times for the left and for the right side of surgery group.

Table 114: Overall T-test results of time for every side of surgery, in Inhibtion

side of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
right	1.28	4	76	.28
left	0.59	4	71	.67

The estimated marginal means are presented in the Appendix 8. Simple contrasts revealed no significant difference between the left and the right hemisphere surgery group at any evaluation time. However, the profile plot and the mean differences show, that the left hemisphere group always performs better than the right hemisphere group by 3.48 to 6.49 standard score points. The standard errors are large and the group sizes rather small, probably accounting for the non-significance of the mean differences between both groups.

Table 115: Simple contrasts between the left and right surgical groups for each postsurgical evaluation time, in Inhibition

Time	side of surgery Simple Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	right - left	-6.49	3.58	-1.81	84	.07
6 mo	right - left	-4.15	3.75	-1.11	94	.27
12 mo	right - left	-3.48	4.04	-0.86	106	.39
24 mo	right - left	-5.24	3.99	-1.32	102	.19
60 mo	right - left	-4.68	4.59	-1.01	113	.32

Note. pre = presurgical evaluation, mo = months post-surgery

To analyze the development of Inhibition capacities over time, in regard of the hemisphere on which surgery was performed, pairwise comparisons were conducted. For the right hemisphere operated group, no significant changes happened between evaluations.

Table 116: Pairwise comparisons of Inhibition scores in standard scores between the presurgical evaluation and each postsurgical evaluation and between consecutive evaluation times for each surgical side.

side of surgery	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
	pre - 6 mo	-3.84	2.25	-1.71	70	.09
	pre - 12 mo	-3.91	2.85	-1.37	71	.17
	pre - 24 mo	-4.51	2.87	-1.57	78	.12
right	pre - 60 mo	-5.02	3.06	-1.64	86	.11
	6 mo - 12 mo	-0.07	2.93	-0.02	70	.98
	12 mo - 24 mo	-0.60	3.30	-0.18	73	.86
	24 mo - 60 mo	-0.51	3.56	-0.14	85	.89
	pre - 6 mo	-1.51	2.35	-0.64	66	.52
	pre - 12 mo	-0.91	2.30	-0.39	67	.70
	pre - 24 mo	-3.27	2.32	-1.41	69	.16
left	pre - 60 mo	-3.16	3.44	-0.92	83	.36
	6 mo - 12 mo	0.60	2.41	0.25	67	.81
	12 mo - 24 mo	-2.36	2.28	-1.04	67	.30
	24 mo - 60 mo	0.11	3.27	0.03	81	.97

Note. pre = presurgical evaluation, mo = months post-surgery

3.3.5.3. IV Etiology. The interaction effect Time x etiology did not reach significance and neither did the main effect of etiology and of time. The F-Tests for the main and interaction effects are reported in the following table:

Table 117: F-Tests for fixed effects Time, etiology and their interaction, in Inhibition

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.82	4	53	.14
etiology	1.38	6	43	.24
Time x etiology	1.12	18	54	.36

At the 12 months post-surgery evaluation, the difference between etiology groups showed a tendency towards significance, shown in the overall F-tests, but not at other evaluation times. The overall F-Tests of time showed significant differences within the etiology group ‘other’, when comparing the means of all the testing times.

Table 118: Overall F-test results of etiology for every evaluation time in Inhibition

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.79	6	72	.58
6 mo	1.70	5	82	.74
12 mo	2.45	4	92	.05
24 mo	0.91	5	81	.48
60 mo	0.91	4	97	.46

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 119: Overall F-test results of time for every etiology group in Inhibition

etiology	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
MCD	1.39	4	59	.25
tumor	0.63	4	57	.64
dual pathology	1.93	4	54	.12
vascular malformation	0.64	3	50	.59
gliosis	0.63	2	50	.54
mesial temporal sclerosis	0.58	4	54	.68
other	6.79	1	50	**.012**

Note. MCD = malformation of cortical development, bold print = significant result

To further analyze these findings, the marginal means are presented in the Appendix 8. No data was available for some groups at various evaluation times: 6 months after surgery, the data for the 'other' group was missing; at 12 months evaluation data for the 'other' and the 'gliosis' groups was unavailable; 24 months past surgery, data was again missing for the 'other' group, and 60 months after surgery, no data could be retrieved for the 'vascular malformation' and the 'gliosis' groups.

To look at the Inhibition abilities for the etiology groups at the 5 testing times, deviation contrasts were conducted (Appendix 8). Prior to surgery, none of the groups significantly differed from the mean of the cohort, but 6 months after surgery, the MCD group was 9.45 standard score points below the mean of the cohort, which was significant. At 12 month post-surgery, the MCD group was 10.49 standard score points below the mean of the cohort. At 24 and 60 months after surgery, no group significantly differed from the mean of the cohort.

To examine the development of Inhibition across the 5 testing times, pairwise comparisons were performed (Appendix 8). No significant changes could be observed within the mesial temporal sclerosis group, as well as within the tumor, the vascular malformation and the gliosis group. In the MCD group, an increase of 6.10 standard score points, which showed a tendency towards significance, could be observed between 12 and 24 months after surgery,

$t(53) = -1.96$, $p = .055$. There was a significant increase in the dual pathology group of 7.95 standard score points between the presurgical and the first post-surgical evaluation, $t(52) = -2.63$, $p = .011$. The etiology group 'other', which has a very small sample size is only available before and 60 months after surgery, shows a significant growth of standard score points between the two evaluations, $t(50) = -2.61$, $p = .012$.

3.3.5.4. IV Surgery Type: In the F-tests for fixed effects, the effects of surgery type, time and interaction of time x surgery type did not reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 120: F-Tests for fixed effects Time, surgery type and their interaction in Inhibition

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.37	4	56	.26
Surgery type	1.47	5	47	.22
Time x surgery type	1.39	19	56	.17

At the 60 months post-surgery evaluation, the differences between surgery groups were significant, as shown in the overall F-tests of surgery type, but not at other evaluation times. The overall F-Tests of time showed significant differences within the surgery group 'standard temporal resection ± AHE' and a tendency towards significance could be observed in the 'temporal tailored resection + AHE', when comparing the means of all testing times.

Table 121: Overall test results of surgery type for every evaluation time, in Inhibition

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.33	5	83	.89
6 mo	1.21	5	96	.31
12 mo	1.83	5	96	.11
24 mo	1.58	5	96	.17
60 mo	2.79	4	97	**.030**

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Table 122: Overall test results of time for every etiology group in Inhibition

type of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
lesionectomy	1.35	4	58	.26
intralobar tailored resection	1.99	4	59	.11
multilobar tailored resection	0.55	4	58	.70
AHE	0.36	4	51	.83
standard temporal resection ± AHE	2.60	4	55	**.046**
temporal tailored resection + AHE	2.62	3	57	.06

Note. bold print = significant result, AHE = amygdalohippocampectomy

Deviation contrasts were conducted to analyze the Inhibition abilities for all surgery groups at the 5 evaluation times. At the presurgical evaluation, as well as at the 6 months post-surgery testings, no significant differences could be observed between the surgery groups. However, the multilobar tailored resection group showed a tendency towards significance at the first postsurgical evaluation. At 12 months after surgery, the multilobar tailored resection group was 13.26 standard score points lower than the mean of the cohort, which was then significant. 24 months after surgery, there was a significant difference between the temporal tailored resection group and the mean of the cohort, the resection group scoring 9.71 standard score points less than the mean. At 60 months after surgery, the multilobar tailored resection group was again significantly lower than the mean of the cohort, this time by 12.41 standard score points.

Table 123: Deviation contrasts in Inhibition between the mean of the cohort and the different surgery type groups, in standard scores.

Time	type of surgery Deviation Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	lesionectomy - Mean	0.86	3.76	0.23	80	.82
	intralobar tailored resection - Mean	-1.70	3.95	-0.43	66	.67
	multilobar tailored resection - Mean	-4.61	4.40	-1.05	83	.30
	AHE - Mean	5.29	6.96	0.76	57	.45
	standard temporal resection ± AHE - Mean	1.12	3.65	0.31	67	.76
	temporal tailored resection + AHE - Mean	-0.97	3.88	-0.25	65	.80
6 mo	lesionectomy - Mean	0.38	3.83	0.10	84	.92
	intralobar tailored resection - Mean	-3.49	4.22	-0.83	78	.41
	multilobar tailored resection - Mean	-8.53	4.44	-1.92	85	.058
	AHE - Mean	6.04	7.87	0.77	80	.45
	standard temporal resection ± AHE - Mean	4.96	3.80	1.30	75	.20
	temporal tailored resection + AHE - Mean	0.64	4.23	0.15	79	.88
12 mo	lesionectomy - Mean	-0.14	3.77	-0.04	83	.97
	intralobar tailored resection - Mean	4.13	4.34	0.95	83	.34
	multilobar tailored resection - Mean	-13.26	4.66	-2.85	92	**.005**
	AHE - Mean	5.48	6.99	0.78	58	.44
	standard temporal resection ± AHE - Mean	-1.19	3.99	-0.30	83	.77
	temporal tailored resection + AHE - Mean	4.98	4.70	1.06	92	.29
24 mo	lesionectomy - Mean	5.23	3.79	1.38	82	.17
	intralobar tailored resection - Mean	0.70	4.26	0.16	80	.87
	multilobar tailored resection - Mean	-6.63	6.24	-1.06	90	.29
	AHE - Mean	7.66	7.03	1.09	59	.28
	standard temporal resection ± AHE - Mean	2.76	3.86	0.72	78	.48
	temporal tailored resection + AHE - Mean	-9.71	4.69	-2.07	93	**.041**
60 mo	lesionectomy - Mean	3.47	4.30	0.81	94	.42
	intralobar tailored resection - Mean	2.13	4.95	0.43	91	.67
	multilobar tailored resection - Mean	-12.41	4.24	-2.93	79	**.004**
	AHE - Mean	-1.03	7.66	-0.14	81	.89
	standard temporal resection ± AHE - Mean	7.84	5.14	1.53	97	.13

Note. pre = presurgical evaluation, mo = months post-surgery, AHE = amgygdalohippocampectomy

Pairwise comparisons were conducted for each surgery group, to look for significant differences of Inhibition within each group, across evaluation times. The ‘intralobar tailored resection’ group differed significantly with an increase of 8.14 standard score points between the presurgical and the 12 months post-surgical evaluation. The ‘standard temporal ± AHE’ group also showed significant increases, of 6.43 standard score points when comparing the presurgical and the first postsurgical evaluation and of 11.69 points when comparing the

presurgical and the 60 months post-surgery evaluation. The 'temporal tailored resection' group was the only group to show a significant postsurgical decrease: This group lost 13.88 points between the 12 and the 24 months postsurgical evaluations. All other comparisons were not significant.

Table 124: Pairwise comparisons of Inhibition scores in standard scores between the presurgical evaluation and every post-surgical evaluation and between consecutive evaluation times, for every type of surgery.

type of surgery	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
lesionectomy	pre - 6 mo	-2.11	3.53	-0.60	57	.55
	pre - 12 mo	-1.31	3.47	-0.38	56	.71
	pre - 24 mo	-7.50	3.87	-1.94	65	.057
	pre - 60 mo	-7.58	4.56	-1.66	63	.10
	6 mo - 12 mo	0.80	3.59	0.22	57	.82
	12 mo - 24 mo	-6.13	3.45	-1.80	58	.08
	24 mo - 60 mo	-0.09	3.83	-0.02	56	.98
intralobar tailored resection	pre - 6 mo	-0.80	3.29	-0.24	51	.81
	pre - 12 mo	-8.14	3.58	-2.28	52	**.027**
	pre - 24 mo	-5.52	3.29	-1.68	51	.10
	pre - 60 mo	-8.80	5.40	-1.63	81	.11
	6 mo - 12 mo	-7.34	3.87	-1.90	52	.06
	12 mo - 24 mo	2.62	3.87	0.68	52	.50
	24 mo - 60 mo	-3.28	5.55	-0.59	79	.56
multilobar tailored resection	pre - 6 mo	1.32	4.05	0.33	52	.75
	pre - 12 mo	6.34	4.99	1.27	58	.21
	pre - 24 mo	-1.11	7.21	-0.15	56	.88
	pre - 60 mo	2.83	4.70	0.60	69	.55
	6 mo - 12 mo	5.02	5.02	1.00	58	.32
	12 mo - 24 mo	-7.44	6.85	-1.09	53	.28
	24 mo - 60 mo	3.93	6.68	0.59	55	.56
AHE	pre - 6 mo	-3.34	6.99	-0.48	52	.63
	pre - 12 mo	-2.50	5.43	-0.46	51	.65
	pre - 24 mo	-5.50	5.43	-1.01	51	.32
	pre - 60 mo	1.34	6.99	0.19	52	.85
	6 mo - 12 mo	0.84	6.99	0.12	52	.90
	12 mo - 24 mo	-3.00	5.43	-0.55	51	.58
	24 mo - 60 mo	6.84	6.99	0.98	52	.33
standard temporal resection ± AHE	pre - 6 mo	-6.43	2.94	-2.18	52	**.034**
	pre - 12 mo	0.01	3.41	0.01	54	.99
	pre - 24 mo	-4.77	3.24	-1.47	57	.15
	pre - 60 mo	-11.69	4.97	-2.35	56	**.022**
	6 mo - 12 mo	6.43	3.54	1.82	54	.08

	12 mo - 24 mo	-4.77	3.43	-1.39	53	.17
	24 mo - 60 mo	-6.92	5.61	-1.24	61	.22
temporal tailored resection + AHE	pre - 6 mo	-4.19	3.82	-1.10	61	.28
	pre - 12 mo	-8.26	4.74	-1.74	62	.09
	pre - 24 mo	5.62	4.39	1.28	58	.21
	6 mo - 12 mo	-4.07	4.19	-0.97	52	.34
	12 mo - 24 mo	13.88	5.17	2.69	56	**.010**

Note. pre = presurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy, bold print = significant result

3.3.5.5. IV Localization. Neither the effect of the interaction time x localization nor the effect of time were significant. The main effect of localization was significant. The F-Tests for the main and interaction effects are reported in the following table:

Table 125 : F-Tests for fixed effects Time, localization and their interaction, in Inhibition

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	2.05	4	67	.10
localization	2.64	4	52	**.044**
Time * localization	1.00	12	68	.46

Note. bold print = significant result

The overall F-test results of localization showed significant differences between the Inhibition capacities of the localization groups at 12 months after surgery as well as at 60 months after surgery. The overall F-test results of time showed no significant differences between evaluation times within each localization group.

Table 125: Overall test results of localization for every evaluation time in Inhibition

time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.44	3	105	.73
6 mo	2.36	3	104	.09
12 mo	3.48	3	105	**.019**
24 mo	1.04	3	105	.38
60 mo	3.53	4	105	**.010**

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Table 126: Overall test results of time for every localization group in Inhibition

localization	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
frontal	1.07	4	73	.38
temporal	1.44	4	64	.23
parietal	1.80	3	63	.16
insular	2.51	1	59	.12
multilobar	.53	4	69	.72

Estimated marginal means are presented in a table in the Appendix 8. At all evaluation times, there was no data available for the occipital localization group. Data from the insular localization group was only collected 6 and 60 months after surgery.

Deviation contrasts were conducted for all localization groups at the 5 testing times to analyze the Inhibition performance. At presurgical evaluation and 24 months after surgery, no deviation contrast reached significance. 6 months post-surgery the temporal localization group was significantly above the mean of the cohort, by 8.77 standard score points. Before surgery and at the following evaluations, the temporal localization group did not differ significantly from the cohort. The parietal and multilobar localization groups differed significantly 12 months after surgery: The parietal group was significantly 12.33 standard score points above the mean and the multilobar group was significantly 13.37 points below the mean of the cohort. At 24 months past surgery both groups were above and below the mean, respectively, but the difference to the mean did not reach significance. However, 60 months after surgery, the parietal group was significantly above the mean by 19.21 points. Also, the multilobar group was again significantly below the mean by 13.42 points.

Table 127 : Deviation contrasts in Inhibition between the mean of the cohort and the localization groups for every evaluation time in standard scores.

Time	localization Deviation Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	frontal - Mean	-0.80	3.60	-0.22	90	.83
	temporal - Mean	1.63	3.10	0.53	94	.60
	parietal - Mean	3.00	6.62	0.45	103	.65
	multilobar - Mean	-3.83	4.25	-0.90	97	.37
6 mo	frontal - Mean	2.85	4.10	0.70	76	.49
	temporal - Mean	8.77	3.60	2.44	73	**.017**
	multilobar - Mean	-2.49	4.57	-0.55	83	.59
	insular - Mean	-9.14	8.38	-1.09	63	.28
12 mo	frontal - Mean	-0.40	3.76	-0.11	96	.92
	temporal - Mean	1.44	3.05	0.47	92	.64
	parietal - Mean	12.33	5.57	2.22	83	**.029**
	multilobar - Mean	-13.37	4.33	-3.09	101	**.003**
24 mo	frontal - Mean	0.15	3.75	0.04	99	.97
	temporal - Mean	-0.58	3.18	-0.18	99	.86
	parietal - Mean	8.55	5.21	1.64	73	.11
	multilobar - Mean	-8.12	5.83	-1.39	98	.17
60 mo	frontal - Mean	-0.67	5.39	-0.12	93	.90
	temporal - Mean	-0.02	4.18	-0.01	101	.99
	parietal - Mean	19.21	7.37	2.61	101	**.011**
	multilobar - Mean	-13.42	4.49	-2.99	82	**.004**
	insular - Mean	-5.10	9.08	-0.56	65	.58

Note. pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Pairwise comparisons were performed to analyze the evolution of Inhibition capacities for the different localization groups across the postoperative timespan (Appendix 8). The frontal and multilobar localization groups had no significant variation in Inhibition abilities over time. The insular group had data available only 6 and 60 months after surgery and showed no significant change between both evaluations. In the temporal surgery group, the comparison between presurgical status and status 6 months after surgery reached significance, $t(63) = -2.19$, $p = 0.033$, in favor of a better performance by 4.55 standard score points 6 months after surgery. 60 months after surgery, the Inhibition abilities compared to the presurgical status had not changed significantly, remaining at 4.71 points difference, $t(64) = -1.44$, $p = 0.16$. In the parietal surgery group, the comparison between presurgical level and the long-term outcome of 60 months past surgery reached significance, $t(66) = -2.31$, $p = 0.024$, the Inhibition capacities gaining 22.58 points on average over the time span.

3.3.5.6. IV Age at Onset. The effect of age at onset was significant, $F(1, 50) = 8.48$, $p = .005$. The effect of time and the interaction effect time x age at onset did not reach significance, $F(4, 76) = 0.51$, $p = .73$ and $F(4, 73) = 0.42$, $p = .80$.

As age at onset is a metric variable, no estimated marginal means can be calculated for it, instead the regression coefficient is interpreted:

Table 128 : Regression coefficient ´age at onset´ for Inhibition for the 5 evaluation times

time	*β*	*p*
Presurgical evaluation = baseline	0.83	**.027**
6 months	0.66	
12 months	1.38	
24 months	1.10	
60 months	1.08	

To calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. At baseline, the coefficient is 0.83, which is significant, $t=2.26$, $p = .027$. Precisely, at the presurgical evaluation, with every year a patient is older at onset of epilepsy, its Inhibition is 0.83 standard score points higher. The influence of the age at onset of epilepsy varies a little across evaluation times: At the 6 months postsurgical evaluation, the Inhibition ability is 0.66 standard score points higher for every year a patient is older at onset. At 12 months after surgery the Inhibition capacity is rising by 1.38 points with every year a patient is older at onset, at 24 months it's 1.10 points more per year older at the start of epilepsy, and at 60 months after surgery it's 1.08 points increase per year older at onset.

3.3.5.7. IV Duration of Epilepsy (in Years). The effect of duration of epilepsy was significant. Neither the effect of time nor the interaction effect Time x duration of epilepsy reached significance, meaning the duration of epilepsy at surgery influences the patient's Inhibition independently of passing time. The F-Tests for the main and interaction effects are reported in the following table:

Table 129: F-Tests for fixed effects Time, duration of epilepsy and their interaction, in Inhibition

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	1.55	4	76	.20
Duration of epilepsy (in years)	7.55	1	52	**.008**
Time x duration of epilepsy	0.91	4	76	.46

Because duration of epilepsy is a continuous variable no estimated marginal means can be calculated, the regression coefficient is interpreted:

Table 130: Regression coefficient `duration of epilepsy´ for Inhibition for the 5 evaluation times

time	*β*	*p*
Presurgical evaluation = baseline	-0.79	**.033**
6 months	-0.69	
12 months	0.57	
24 months	-1.26	
60 months	-1.02	

Note. bold print = significant result

To calculate the regression coefficient, the baseline reference category is the presurgical evaluation, and is set at time = 0. The coefficient at baseline is -0.79, which is significant, t=-2.17 p = .033, as expected. This means that at the presurgical evaluation, with every year a patient has been having epilepsy, its Inhibition ability is 0.79 standard score points lower. Also as expected, the influence of the duration of the epilepsy varies very little across evaluation times: At the 6 months postsurgical evaluation, the Inhibition ability is 0.69 standard score points lower for every year a patient has been having epilepsy. At 12 months after surgery, Inhibition ability is just 0.57 points lower with every year, at 24 months it's -1.26 points decrease per year of epilepsy duration. And at 60 months after surgery, it's -1.02 points less per year of having had epilepsy at surgery.

3.3.5.8. IV Seizure Outcome. There was no significant effect of time, of the seizure outcome or of its interaction. The F-Tests for the main and interaction effects are reported in the following table:

Table 131: F-Tests for fixed effects Time, Seizure outcome (in Engel categories) and their interaction, in Inhibition

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.65	3	79	.59
Engel	0.04	1	88	.84
Time x Engel	0.49	3	80	.69

The seizure outcome only has 2 features (Engel 1a, Engel >1a), so no overall F-Test was conducted, because it is the same as the F-tests for main effects. The estimated marginal means are presented in the Appendix 8. Simple contrasts were performed to analyze the evolution of

the Inhibition abilities over time in the 2 different Seizure outcome groups. There were no significant differences in Inhibition between the two patient groups across evaluation times.

Table 132: Simple contrasts between seizure outcome groups for each postsurgical evaluation time in Inhibition

Time	Engel Simple Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
6 mo	1a - > 1a	0.16	4.20	0.04	78	.97
12 mo	1a - > 1a	1.76	5.71	0.31	77	.76
24 mo	1a - > 1a	-4.88	4.01	-1.22	85	.23
60 mo	1a - > 1a	0.95	4.15	0.23	93	.82

Note. mo = months post-surgery, Engel = seizure outcome in Engel categories

Other pairwise comparisons, comparing the performance at the different evaluation times for each Seizure outcome group separately, were conducted. When comparing the different evaluation times in consecutive order, no significant differences could be observed, neither for the seizure free (1a), nor for the group of patients which still had seizures (>1a).

Table 133: Pairwise comparisons between consecutive evaluation times for each seizure outcome group in Inhibition

Seizure outcome	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
1a	6 mo - 12 mo	0.05	2.05	0.03	67	.98
	12 mo - 24 mo	-0.85	2.07	-0.41	67	.68
	24 mo - 60 mo	-1.22	3.11	-0.39	80	.70
>1a	6 mo - 12 mo	1.66	6.11	0.27	71	.79
	12 mo - 24 mo	-7.48	6.57	-1.14	81	.26
	24 mo - 60 mo	4.60	4.57	1.01	88	.32

3.3.5.9. IV Antiseizure Drug (ASM) Load. There were no significant main effects of time, of ASM load and of its interaction Time x ASM load. The F-Tests for the main and interaction effects are reported in the following table:

Table 134: F-Tests for fixed effects Time, antiseizure drug load and their interaction, in Inhibition

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.24	4	75	.92
ASM load	2.15	2	88	.12
Time x ASM load	0.32	6	74	.93

Note. ASM = Antiseizure drugs

The overall F- tests showed no significant differences between the different ASM load groups at all evaluation times.

Table 135: Overall F-Test results of antiseizure drug load for every evaluation time in Inhibition

Time	*F*	$Df_{Nom.}$	$Df_{Denom.}$	*p*
pre	0.57	1	86	.45
6 mo	0.43	1	79	.52
12 mo	0.43	2	71	.66
24 mo	0.67	2	78	.52
60 mo	1.71	2	89	.19

Note. pre = presurgical evaluation, mo = months post-surgery

The estimated marginal means and standard errors of time are presented in the Appendix 8. There were no patients without ASM at the presurgical evaluation and at the 6 months postsurgical evaluation.

To analyze the significant differences that appear to exist between the ASM groups, pairwise comparisons were conducted. Surprisingly, none of the comparisons between any of the ASM groups at any evaluation time reached significance. However, there are constantly superior results for the '1 ASM group', also for the '0 ASM' group. The biggest difference is seen 60 months after surgery, where a difference of 9.94 points is observed between the '0 ASM' and the '>1 ASM' groups, and of 7.8 points between the '1 ASM' and the '>1 ASM' groups. As in other dependent variables seen before, the standard errors are very large, especially at 12 and at 60 months, and the group sizes rather small, probably explaining the non-significance of the comparisons.

Other pairwise comparisons, comparing the performance at the different evaluation times for each ASM group separately, were not conducted, since these did not make sense: it was expected for most patients to change ASM groups with passing time, when (a few) ASM were weaned off after a seizure free period following surgery.

Table 136: Pairwise comparisons of Inhibition scores in standard scores between the antiseizure drug load groups for every evaluation time

Time	ASM Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
pre	1 - > 1	2.54	3.38	0.75	86	.45
6 mo	1 - > 1	1.94	2.97	0.65	79	.52
	1 - > 1	2.80	3.28	0.86	76	.40
12 mo	0 - 1	1.26	7.17	0.18	66	.86
	0 - > 1	4.07	7.29	0.56	67	.58
	1 - > 1	4.21	3.64	1.16	73	.25
24 mo	0 - 1	-1.16	3.82	-0.30	82	.76
	0 - > 1	3.05	4.46	0.68	81	.50
	1 - > 1	7.80	4.71	1.66	105	.10
60 mo	0 - 1	2.14	5.82	0.37	73	.71
	0 - > 1	9.94	6.47	1.54	91	.13

Note. pre = presurgical evaluation, mo = months post-surgery, ASM = antiseizure drug load groups

3.3.6. Multivariate Analysis of Flexibility

The measure ‘Symbol search’, a cumulative measure composed of the subtest results of ‘Symbol search’ from the different Wechsler IQ-test batteries, was used as a dependent variable to evaluate the executive function ‘Flexibility’. Again, time as well as the same set of possible predictors were used as independent variables. The measure ‘Flexibility’ is indicated in scaled score points as used in the Wechsler Intelligence tests (mean = 10, standard deviation = 3). 141 values of 55 patients could be included into the following models.

3.3.6.1. IV Presurgical IQ. No significant main effect of time could be found, $F(9, 97) = 0.83$, $p = .51$. However, there was a significant main effect of presurgical IQ, $F(1,60) = 26.60$, $p = <.001$. The interaction time x presurgical IQ on Flexibility capacities was not significant, $F(4, 272) = 01.31$, $p = .27$. Because presurgical IQ is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted.

Table 137: Regression coefficient ´presurgical IQ´ for flexibility for the 5 evaluation times

Time	*β*	*p*
presurgery = baseline	0.15	**< .001**
6 months	0.09	
12 months	0.11	
24 months	0.10	
60 months	0.14	

The baseline reference category is the presurgical evaluation, to calculate the coefficient, and is set at time = 0. The coefficient is 0.15 at baseline, which is significant, t= 4.77, p = <.001. So at the presurgical evaluation, the higher the IQ, the higher is the Flexibility performance. The regression coefficient signifies that with every IQ point difference, the Flexibility performance increases by 0.15 scaled score points. The influence of presurgical IQ does change only minimally across evaluation times: At the 6 months postsurgical evaluation, the Flexibility ability is 0.09 scaled score points higher for every additional IQ point. At 12 months after surgery the Flexibility ability is 0.11 scaled score points higher with every additional IQ point, at 24 months it's 0.10 scaled score points more per additional IQ point and at 60 months after surgery it's 0.14 scaled score points increase per additional IQ point.

3.3.6.2. IV Side of Surgery. The main effect of side of surgery was significant, the effects of time and of the interaction time x side of surgery were not. The F-Tests for the main and interaction effects are reported in the following table:

Table 138 : F- Tests for fixed effects Time, side of surgery and their interaction, in flexibility

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.28	4	99	.89
side of surgery	5.07	1	66	**.028**
Time x side of surgery	0.37	4	99	.83

Note. bold print = significant result

The overall F-Test of side of surgery showed significant differences at 12 and 24 months after surgery when comparing the means of the two side of surgery groups. At other evaluation times, no significant differences between the means of the two groups could be found.

Table 139 : Overall test results of side of sugery for every evaluation time in Flexibility

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	2.65	1	109	.11
6 mo	1.00	1	134	.32
12 mo	4.42	1	116	**.038**
24 mo	6.29	1	123	**.013**
60 mo	0.34	1	112	.56

Note. pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

The overall F-Test of time showed no significant difference between the means of the 5 evaluation times for either side of surgery.

Table 140: Overall F-test results of time for every side of surgery in Flexibility

side of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
right	0.09	4	100	.99
left	0.70	4	100	.59

To examine the significant effect of time, the estimated marginal means are presented in the Appendix 9. Simple contrasts revealed a significant difference between the left and the right hemisphere surgery group at 12 and at 24 months post-surgery, $t(116) = -2.10$, $p = .038$ and $t(123) = -2.51$, $p = .013$. The left hemisphere group obtained results, which were 2.03 to 2.52 scaled score points higher than those obtained by the right hemisphere group.

Table 141 : Simple contrasts between side of surgery groups for each evaluation time in Flexibility

Time	side of surgery Simple Contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	right - left	-1.50	0.92	-1.63	109	.11
6 mo	right - left	-1.16	1.17	-1.00	134	.32
12 mo	right - left	-2.03	0.96	-2.10	116	**.038**
24 mo	right - left	-2.52	1.01	-2.51	123	**.013**
60 mo	right - left	-1.26	2.17	-0.58	112	.56

Note. bold print = significant result, pre = presurgical evaluation, mo = months post-surgery

Pairwise comparisons were conducted, in regard of the hemisphere on which surgery was performed to analyze the evolution of Flexibility over time. No significant changes appeared neither for the left nor for the right side of surgery group, from before surgery up to 60 months after surgery. The variations in performance varied non-significantly between -0.1

and 1.47 scaled score points for the left side of surgery group, and between -0.12 and 0.38 scaled score points for the right side of surgery group.

Table 142: Pairwise comparisons in Flexibility (in scaled score points) between the presurgical evaluation and the post-surgical evaluation times and between the consecutive evaluations, for each side of surgery

side of surgery	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
	pre - 6 mo	-0.35	0.93	-0.38	94	.71
	pre - 12 mo	-0.12	0.75	-0.17	91	.87
	pre - 24 mo	0.17	0.80	0.22	103	.83
right	pre - 60 mo	0.38	1.90	0.20	95	.84
	6 mo - 12 mo	0.22	0.99	0.23	100	.82
	12 mo - 24 mo	0.30	0.81	0.37	94	.71
	24 mo - 60 mo	0.21	1.93	0.11	98	.91
	pre - 6 mo	-0.01	0.77	-0.01	94	.99
	pre - 12 mo	-0.65	0.67	-0.98	89	.33
	pre - 24 mo	-0.85	0.73	-1.17	95	.25
left	pre - 60 mo	0.62	1.32	0.47	131	.64
	6 mo - 12 mo	-0.64	0.75	-0.86	89	.39
	12 mo - 24 mo	-0.20	0.71	-0.28	89	.78
	24 mo - 60 mo	1.47	1.32	1.11	128	.27

Note. pre = presurgical evaluation, mo = months post-surgery

3.3.6.3. IV Etiology. The main effects of time, etiology and the interaction effect Time x etiology did not reach significance. However, etiology showed a tendency towards significance. There was no data available for the etiology group "other" at all and no data available for the groups 'gliosis' and 'mesial temporal sclerosis' at the 60 months postsurgical evaluation. For the 'vascular' group, there is data available only before surgery and 6 months after surgery.

Table 143 : F-Tests for fixed effects Time, etiology, and their interaction in Flexibility

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.27	4	81	.90
etiology	2.26	5	51	.06
Time x etiology	1.50	15	85	.12

Despite there was no significant interaction or main effect, overall F-tests of time and etiology were conducted exploratively to look out for significant differences, which might be undisclosed due to variations only appearing in a few features and thus not rendering the main

effect significant. The overall F-test of etiology reveals significant differences between etiology groups at the presurgical evaluation. At 12 months there is a tendency towards significance for the different etiology groups. The overall F-tests of time do not show any differences between evaluation times within each etiology group.

Table 144 : Overall F-test results of etiology for every evaluation time in Flexibility

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	2.72	5	111	**.023**
6 mo	1.59	5	120	.17
12 mo	2.22	4	120	.07
24 mo	1.80	4	120	.13
60 mo	0.80	2	120	.45

Note. pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Table 145 : Overall F-Test results of time for every etiology type in Flexibility

etiology	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
MCD	1.80	4	93	.14
tumor	0.26	4	89	.90
dual pathology	1.84	4	84	.13
vascular malformation	0.47	1	73	.50
gliosis	2.19	3	79	.10
mesial temporal sclerosis	0.39	3	73	.76

Note. MCD = malformation of cortical development

To further analyze these findings, the marginal means are presented in the Appendix 9. Deviation contrasts were conducted to analyze the Flexibility capacities for all etiology groups at the 5 testing times. Three groups deviated significantly: the dual pathology group and the mesial temporal sclerosis group before surgery, and the MCD group 12 months after surgery. The dual pathology group deviated significantly by 2.90 scaled score points below the mean of the surgery cohort, $t(92) = -2.54$, $p = .013$, whereas the mesial temporal sclerosis group differed significantly by 5.50 scaled score points above the mean, $t(85) = 2.16$, $p = .034$. 12 months after surgery the MCD group differed significantly by 2.66 scaled score points below the mean of the cohort, $t(9) = -2.72$, $p = .008$.

Table 146 : Deviation contrasts in Flexibility between the mean of the cohort and the etiology groups for every evaluation time in scaled score points.

Time	etiology Deviation Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	MCD - Mean	-1.37	1.04	-1.32	96	.19
	tumor - Mean	0.36	0.98	0.37	90	.71
	dual pathology - Mean	-2.90	1.14	-2.54	92	**.013**
	vascular malformation - Mean	-2.50	2.55	-0.98	85	.33
	gliosis - Mean	0.90	1.31	0.69	93	.49
	mesial temporal sclerosis - Mean	5.50	2.55	2.16	85	**.034**
6 mo	MCD - Mean	-1.75	1.10	-1.59	106	.12
	tumor - Mean	1.49	1.23	1.21	118	.23
	dual pathology - Mean	-0.61	1.28	-0.48	109	.64
	vascular malformation - Mean	-0.48	2.56	-0.19	86	.85
	gliosis - Mean	-2.18	1.51	-1.44	112	.15
	mesial temporal sclerosis - Mean	3.52	2.56	1.38	86	.17
12 mo	MCD - Mean	-2.66	0.98	-2.72	98	**.008**
	tumor - Mean	0.16	0.93	0.18	95	.86
	dual pathology - Mean	-0.88	1.10	-0.80	98	.43
	gliosis - Mean	-0.48	1.24	-0.38	93	.70
	mesial temporal sclerosis - Mean	3.85	2.41	1.60	85	.11
24 mo	MCD - Mean	0.50	1.04	0.49	108	.63
	tumor - Mean	0.82	0.96	0.86	100	.39
	dual pathology - Mean	-1.76	1.07	-1.64	95	.10
	gliosis - Mean	-2.09	1.31	-1.60	102	.11
	mesial temporal sclerosis - Mean	2.53	2.42	1.05	85	.30
60 mo	MCD - Mean	-0.60	1.43	-0.42	105	.68
	tumor - Mean	1.97	1.62	1.21	116	.23
	dual pathology - Mean	-1.37	2.11	-0.65	91	.52

Note. MCD = malformation cognitive development, pre = presurgical evaluation, mo = months post-surgery

The evolution of the Flexibility capacities was analyzed via pairwise comparisons for the different etiology groups across time. The tumor, vascular and mesiotemporal sclerosis groups showed no significant changes in Flexibility performance across time, however for the latter two groups, data was not available for all 5 evaluation times. The MCD group showed significant change once, an increase of 2.48 scaled score points between 12 and 24 months after surgery. Between 24 and 60 months after surgery the Flexibility performance dropped again by 2.21 scaled score points for this group. However, this drop in performance was not significant. A significant increase of 2.67 scaled score points when comparing the presurgical and the 12 months post-surgery evaluation could be observed in the dual pathology group. However, this progress slowly decreased again afterwards. 60 months after surgery the Flexibility abilities was just of 0.4 scaled score points above the presurgical state, a not significant difference. In the gliosis group, for which data was available up to 24 months after surgery, a significant drop of 3.02 scaled score points in Flexibility abilities was noted when comparing the presurgical with the 24 months postsurgical level of ability. However, in between these evaluation times, the Flexibility performance was very inconsistent.

Table 147: Pairwise comparisons between the presurgical evaluation and postsurgical evaluation times and between consecutive evaluation times for every etiology group, in Flexibility

etiology	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p*
MCD	pre - 6 mo	0.40	1.02	0.39	88	.70
	pre - 12 mo	0.63	0.93	0.68	82	.50
	pre - 24 mo	-1.85	1.07	-1.73	90	.09
	pre - 60 mo	0.36	1.47	0.25	119	.81
	6 mo - 12 mo	0.23	0.98	0.24	81	.81
	12 mo - 24 mo	-2.48	1.00	-2.47	80	**.016**
	24 mo - 60 mo	2.21	1.48	1.50	119	.14
tumor	pre - 6 mo	-1.10	1.14	-0.97	82	.34
	pre - 12 mo	-0.46	0.78	-0.59	78	.56
	pre - 24 mo	-0.43	0.85	-0.51	87	.61
	pre - 60 mo	-0.47	1.88	-0.25	113	.80
	6 mo - 12 mo	0.65	1.17	0.55	84	.58
	12 mo - 24 mo	0.02	0.85	0.03	82	.98
	24 mo - 60 mo	-0.04	1.91	-0.02	112	.98
dual pathology	pre - 6 mo	-2.27	1.21	-1.87	76	.07
	pre - 12 mo	-2.67	1.08	-2.48	75	**.016**
	pre - 24 mo	-1.11	1.09	-1.01	84	.31
	pre - 60 mo	-0.40	3.14	-0.13	86	.90
	6 mo - 12 mo	-0.40	1.27	-0.32	79	.75
	12 mo - 24 mo	1.57	1.12	1.40	82	.17
	24 mo - 60 mo	0.71	3.14	0.23	86	.82
vascular malformation	pre - 6 mo	-2.00	2.92	-0.69	73	.50
gliosis	pre - 6 mo	3.09	1.63	1.90	84	.06
	pre - 12 mo	0.72	1.36	0.53	81	.60
	pre - 24 mo	3.02	1.47	2.06	82	**.043**
	6 mo - 12 mo	-2.38	1.56	-1.53	77	.13
	12 mo - 24 mo	2.30	1.40	1.64	75	.11
mesial temporal sclerosis	pre - 6 mo	2.00	2.92	0.69	73	.50
	pre - 12 mo	1.00	2.92	0.34	73	.73
	pre - 24 mo	3.00	2.92	1.03	73	.31
	6 mo - 12 mo	-1.00	2.92	-0.34	73	.73
	12 mo - 24 mo	2.00	2.92	0.69	73	.50

Note. pre = presurgical evaluation, mo = months post-surgery, MCD = malformation cortical development, bold print = significant result

3.3.6.4. IV Surgery Type. For the IV surgery type analysis of Flexibility, there was no data available for the 'AHE' group. For the groups 'standard temporal resection ± AHE' and 'temporal tailored resection ± AHE' data at 60 months after surgery was missing. In the F-tests for fixed effects, the effects of surgery type and interaction Time x surgery type did not reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 148 : F-Tests for fixed effects Time, surgery type and their interaction in Flexibility

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.42	4	83	.80
Surgery type	0.90	4	52	.47
Time x surgery type	1.37	14	84	.19

The overall F-tests of surgery type were all not significant (Appendix 9). The overall F-test of time revealed significant differences between evaluation times in Flexibility for the 'standard temporal resection ± AHE' group. The estimated marginal means and standard error for time are reported in the Appendix 9 as well.

Table 149: Overall F-test results of time for every surgery group in Flexibility

type of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
lesionectomy	0.32	4	93	.86
intralobar tailored resection	0.52	4	93	.72
multilobar tailored resection	0.72	4	83	.58
standard temporal resection ± AHE	4.22	3	73	**.008**
temporal tailored resection + AHE	0.75	3	78	.53

Note. AHE = amygdalohippocampectomy, bold print = significant result

To analyze the Flexibility abilities for all surgery groups at the 5 testing times, deviation contrasts were conducted (Appendix 9). The 6 features of surgery type were compared with the mean of all features combined, for each of the testing times. At the 6,12, 24 and 60 months appointments, no significant differences could be observed between the surgery groups. At the presurgical evaluation, the 'standard temporal resection ± AHE' group scores were 2.65 scaled score points significantly lower than the mean of the cohort, in concordance with the overall F-test results for surgery type.

For each surgery group, pairwise comparisons were conducted within each group, to look for significant differences of Flexibility across time. All results were not significant, but in one group: in the 'standard temporal resection ± AHE' group a significant increase of 2.57

scaled score points happened between the presurgical evaluation and the 6 months post-surgical evaluation, and also a significant increase of 4.40 scaled score points between the presurgical evaluation and the 12 months evaluation and 3.07 scaled score points, when comparing the presurgical to the 24 months post-surgical evaluation. Looking chronologically, the increase of 1.83 points between 6 and 12 months was not big enough to become significant, as well as the decrease of 1.33 points between 12 and 24 months after surgery. Results of these pairwise comparisons can be looked up in Appendix 9.

3.3.6.5. IV Localization. There was no data available at the 60 months evaluation for the temporal and for the occipital group. The main effects time and localization as well as the interaction effect time x localization were not significant. The F-Tests for the main and interaction effects are reported in the following table:

Table 150: F-Tests for fixed effects Time, localization and their interaction in Flexibility

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.07	4	84	.99
localization	1.76	4	54	.15
Time * localization	1.25	14	82	.26

The overall F-test results of localization showed no significant differences between the flexibilty abilities of the localization groups at any evaluation time. The overall F-test results of time also showed no significant differences between evaluation times within the different localization groups (Appendix 9).

Estimated marginal means are presented in a table in the Appendix 9. Deviation contrasts were conducted to analyze the Inhibition capacities for all localization groups at the 5 testing times. None of the deviation contrasts were significant.

Table 151 : Deviation contrasts in Flexibility between the mean of the cohort and the localization groups for every evaluation time, in scaled score points

Time	Localization Deviation Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	frontal - Mean	-1.15	0.91	-1.27	95	.21
	temporal - Mean	-0.34	0.80	-0.43	95	.67
	parietal - Mean	-0.11	1.32	-0.08	91	.94
	occipital - Mean	1.82	1.52	1.20	83	.23
	multilobar - Mean	-0.22	1.06	-0.21	89	.84
6 mo	frontal - Mean	-0.60	1.18	-0.51	122	.61
	temporal - Mean	-0.55	0.95	-0.58	117	.56
	parietal - Mean	2.80	1.67	1.68	120	.10
	occipital - Mean	0.59	1.75	0.33	108	.74
	multilobar - Mean	-2.24	1.41	-1.58	121	.12
12 mo	frontal - Mean	-1.11	1.03	-1.08	112	.29
	temporal - Mean	0.72	0.81	0.88	97	.38
	parietal - Mean	1.94	1.45	1.34	106	.18
	occipital - Mean	-0.26	1.53	-0.17	84	.86
	multilobar - Mean	-1.29	1.13	-1.14	98	.26
24 mo	frontal - Mean	0.23	1.09	0.21	119	.84
	temporal - Mean	0.40	0.93	0.44	117	.66
	parietal - Mean	4.11	2.10	1.96	116	.053
	occipital - Mean	-2.26	1.77	-1.28	109	.20
	multilobar - Mean	-2.48	1.33	-1.87	119	.06
60 mo	frontal - Mean	-1.49	1.52	-0.98	100	.33
	parietal - Mean	3.27	1.75	1.87	106	.06
	multilobar - Mean	-1.79	2.24	-0.80	86	.43

Note. Pre = presurgical evaluation, mo = months post-surgery,

Pairwise comparisons were conducted to further analyze the Flexibility capacities for the different localization groups across the postoperative timespan (Appendix 9). The detailed results can be seen in figure below. All but one pairwise comparison in the occipital group, were not significant. In the occipital group, a significant decrease of 3.96 scaled score points happened between the presurgical and the 24 months postsurgical evaluation. Looking at chronologically, there was a slow but steady decrease in this group since surgery.

3.3.6.6. IV Age at Onset: The effect of age at onset and the effect of time, as well as the interaction effect time x age at onset reach significance. The F-Tests for the main and interaction effects are reported in the following table:

Table 152 : F-Tests for fixed effects Time, age at onset and their interaction in Flexibility

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	3.03	4	107	**.021**
Age at onset	5.76	1	91	**.018**
Time x age at onset	2.80	4	101	**.030**

Note. Bold print = significant results

Because age at onset is a metric variable no estimated marginal means can be calculated for it, instead the regression coefficient is interpreted:

Table 153 : Regression coefficient ´age at onset´ for Flexibility for the 5 evaluation times

time	*β*	*p*
Presurgical evaluation = baseline	0.33	**.003**
6months	0.23	
12 months	-0.03	
24 months	0.11	
60 months	0.45	

Note. bold print = significant result

As before, to calculate the regression coefficient, the baseline reference category is the presurgical evaluation. At the baseline, the coefficient is 0.33, which is significant, $t = 3.06$, $p = .003$. So at the presurgical evaluation, with every year a patient is older at onset of epilepsy, its Flexibility is 0.33 scaled score points higher. The influence of the age at onset of epilepsy varies across evaluation times: At the 6 months postsurgical evaluation, the Flexibility ability is 0.23 scaled score points higher for every year a patient is older at onset. 12 months after surgery the age at onset has almost no influence on the Flexibility capacities, with a decrease of 0.03 scaled score points with every year a patient is older at onset. 24 months after surgery it's only 0.11 scaled score points more per year older at the start of epilepsy, and at 60 months after surgery it's an increase of 0.45 scaled score points per year older at onset. For this variable too, depending on time passing after surgery, the influence of the age at onset varies, but the variations are rather minimal. The interaction effect between time and age at onset suggests that the effect of age at onset on Flexibility was significantly modified by the factor time.

3.3.6.7. IV Duration of Epilepsy (in Years). The interaction effect time x duration of epilepsy was not significant, as well as the main effects of time. However, the main effect of duration of epilepsy was significant. The F-Tests for the main and interaction effects are reported in the following table:

Table 154 : F-Test for fixed effects Time, duration of epilepsy (in years)` and their interaction in Flexibility

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.98	4	107	.42
Duration of epilepsy (in years)	4.16	1	96	**.044**
Time x duration of epilepsy	2.12	4	103	.08

Note. bold print = significant result

Because duration of epilepsy is a continuous variable no estimated marginal means can be calculated, but instead the regression coefficient is interpreted:

Table 155 : Regression coefficient ´duration of epilepsy (in years)´for Flexibility for the 5 evaluation times

time	*β*	*p*
Presurgical evaluation = baseline	-0.46	**<.001**
6 months	-0.42	
12 months	-0.08	
24 months	-0.28	
60 months	-0.28	

Note. bold print = significant result

As previously, to calculate the regression coefficient, the baseline reference category is the presurgical evaluation. At baseline, the coefficient is -0.46, which is significant, *t= -3.84, p* = <.001. This means that at the presurgical evaluation, with every year a patient has been having epilepsy, its Flexibility ability is 0.46 scaled score points lower. The influence of the duration of the illness varies across evaluation times: At the 6 months postsurgical evaluation, the Flexibility ability is 0.42 scaled score points lower for every year a patient has been having epilepsy. At 12 months after surgery Flexibility is just 0.08 scaled score points lower with every year. At 24 months it's 0.28 scaled score points less per year of epilepsy, and at 60 months after surgery it's also 0.28 scaled score points decrease per year of epilepsy duration.

3.3.6.8. IV Seizure Outcome. No significant effect of time, of the seizure outcome (categories Engel 1a, Engel >1a) or of its interaction could be observed. The F-Tests for the main and interaction effects are reported in the following table:

Table 156 : F-Tests for fixed effects Time, Seizure outcome (in Engel categories) and their interaction, in Flexibility

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.43	3	102	.73
Engel	1.59	1	130	.21
Time x Engel	1.32	3	104	.27

Note: Engel = seizure outcome expressed in Engel categories

No overall F-Test could be reported because the seizure outcome only has 2 features, therefore an overall F-Test would be identical as the F-tests for main effects. The estimated marginal means are presented in the Appendix 9. Pairwise comparisons were conducted to analyze the evolution of the Flexibility capacities over time, in regard of the Seizure outcome of the patients, despite no significant main effects. The analyses did not reveal any significant differences in Flexibility between the two patient groups at any evaluation time after surgery. However, the profile plots showed a large difference of 3.89 scaled score points between the 1a and the >1a Seizure outcome groups at the 60 months postsurgical evaluation, in favor of the >1a group.

Table 157 : Pairwise comparison between both seizure outcome groups for every evaluation time in Flexibility

Time	Engel Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p.*
6 mo	1a - > 1a	0.97	1.13	0.86	108	.39
12 mo	1a - > 1a	-0.61	0.94	-0.65	108	.52
24 mo	1a - > 1a	-0.53	0.96	-0.55	113	.58
60 mo	1a - > 1a	-3.89	2.37	-1.64	129	.10

Note. mo = months post-surgery, Engel = seizure outcome expressed in Engel categories.

Other pairwise comparisons, comparing the performance at the 5 evaluation times for each seizure outcome group separately, were conducted. When comparing the 5 evaluation times in consecutive order, no significant differences could be observed, neither for the seizure free (1a), nor for the group of patients which still had seizures (>1a).

Table 158 : Pairwise comparisons between consecutive evaluation times for each seizure outcome group in Flexibility

Seizure outcome	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
1a	6 mo - 12 mo	0.21	0.74	0.28	89	.78
	12 mo - 24 mo	0.26	0.71	0.04	88	.97
	24 mo - 60 mo	2.67	1.61	1.66	125	.10
>1a	6 mo - 12 mo	-1.37	1.15	-1.19	98	.24
	12 mo - 24 mo	0.11	0.97	0.11	93	.91
	24 mo - 60 mo	-0.69	1.91	-0.36	102	.72

Note. mo = months post-surgery

3.3.6.9. IV Antiseizure Drug (ASM) Load. There were no significant effects of time, ASM load or of its interaction Time x ASM load. The F-Tests for the main and interaction effects are reported in the following table:

Table 159 : F-Tests for fixed effects time, antiseizure drug load and their interaction in Flexibility

Source	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
Time	0.71	4	105	.59
ASM load	1.00	2	126	.37
Time x ASM load	0.43	7	105	.88

Note. ASM = antiseizure drug

The overall F- tests showed no significant differences between the different ASM load groups at any testing time.

Table 160: Overall F-test results of antiseizure drug load for the 5 evaluation times in Flexibility

Time	*F*	$Df_{Nom.}$	$Df_{Denom.}$	*p*
pre	0.12	2	114	.88
6 mo	0.60	1	108	.44
12 mo	1.28	2	107	.28
24 mo	0.34	2	109	.71
60 mo	0.53	2	118	.59

Note. pre = presurgical evaluation, mo = months post-surgery

The estimated marginal means are presented in the Appendix 9. Despite there were no significant main effects, pairwise comparisons were conducted to observe the development of Flexibility over time, especially since the visual analysis of the estimated marginal means

showed superior results for the medication free group at 12 and 60 months after surgery. The analysis showed no significant differences between groups at any testing time, even though differences from up to 2.9 scaled score points were found, but with large standard errors and small sample sizes.

Other pairwise comparisons, comparing the performance at the different evaluation times for each ASM group separately, were not conducted, since these did not make sense: it was expected for most patients to change ASM groups with passing time, when (some) ASM were weaned off after a seizure free period following surgery.

Table 161 : Pairwise comparisons between the antiseizure drug load groups for every evaluation time in Flexibility

Time	ASM Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
	0 - 1	0.48	2.83	0.17	114	.87
pre	0 - > 1	0.86	2.80	0.31	116	.76
	1 - > 1	0.38	0.89	0.43	113	.67
6 mo	1 - > 1	0.85	1.09	0.78	108	.44
	0 - 1	2.34	1.63	1.44	103	.15
12 mo	0 - > 1	2.66	1.68	1.59	105	.12
	1 - > 1	0.32	0.94	0.34	112	.74
	0 - 1	-0.25	1.01	-0.25	103	.80
24 mo	0 - > 1	0.91	1.44	0.64	116	.53
	1 - > 1	1.17	1.40	0.83	113	.41
	0 - 1	2.94	2.93	1.00	121	.32
60 mo	0 - > 1	1.71	2.79	0.61	124	.54
	1 - > 1	-1.23	3.09	-0.40	109	.69

Note. pre = presurgical evaluation, mo = months post-surgery, ASM = Antiseizure medication groups

3.3.7. Summary of Multivariate Models of EF

The following tables gives an overview of the different multivariate multilevel models for each EF presented in this chapter.

Table 162: Multivariate multilevel model for the EF Planning: Significance of main effects

Clinical variables	Effect of clinical variable	Effect of time	Interaction effect time x clinical variable
Presurgical IQ	✓***	x	x
Side of surgery	x	✓*	x
Etiology	x	x	x
Surgery type	x	(✓)	x
Localization	✓*	✓*	x
Age at onset	(✓)	✓***	✓*
Duration of epilepsy	✓**	(✓)	x
Seizure outcome	(✓)	x	x
ASM load	✓*	x	x

Note. x = no significant effect; ✓ = significant effect; (✓) = non-significant trend ($p < 0.10$); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 163: Multivariate multilevel model for the EF Problem Solving: Significance of main effects

Clinical variables	Effect of clinical variable	Effect of time	Interaction effect time x clinical variable
Presurgical IQ	✓***	x	x
Side of surgery	✓*	x	x
Etiology	✓*	x	x
Surgery type	x	x	x
Localization	✓*	x	x
Age at onset	✓*	x	x
Duration of epilepsy	✓***	x	x
Seizure outcome	x	x	x
ASM load	x	x	x

Note. x = no significant effect; ✓ = significant effect; (✓) = non-significant trend ($p < 0.1$); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 164: Multivariate multilevel model for the EF Fluency: Significance of main effects

Clinical variables	Effect of clinical variable	Effect of time	Interaction effect time x clinical variable
Presurgical IQ	✓*	✓***	✓**
Side of surgery	✓*	✓*	x
Etiology	✓***	(✓)	x
Surgery type	x	(✓)	x
Localization	x	x	x
Age at onset	✓**	x	x
Duration of epilepsy	✓**	x	x
Seizure outcome	(✓)	x	x
ASM load	x	x	x

Note. x = no significant effect; ✓ = significant effect; (✓) = non-significant trend (p < 0.10), * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 165: Multivariate multilevel model for the EF Working Memory: Significance of main effects

Clinical variables	Effect of clinical variable	Effect of time	Interaction effect time x clinical variable
Presurgical IQ	✓***	x	x
Side of surgery	✓*	✓*	x
Etiology	✓***	x	x
Surgery type	(✓)	(✓)	x
Localization	x	x	x
Age at onset	✓*	x	x
Duration of epilepsy	✓*	x	x
Seizure outcome	x	(✓)	x
ASM load	x	✓	x

Note. x = no significant effect; ✓ = significant effect; (✓) = non-significant trend (p < 0.10); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 166: Multivariate multilevel model for the EF Inhibition: Significance of main effects

Clinical variables	Effect of clinical variable	Effect of time	Interaction effect time x clinical variable
Presurgical IQ	✓**	x	(✓)
Side of surgery	x	x	x
Etiology	x	x	x
Surgery type	x	x	x
Localization	✓*	x	x
Age at onset	✓**	x	x
Duration of epilepsy	✓**	x	x
Seizure outcome	x	x	x
ASM load	x	x	x

Note. x = no significant effect; ✓ = significant effect; (✓) = non-significant trend (p < 0.10); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 167: Multivariate multilevel model for the EF Flexibility: Significance of main effects

Clinical variables	Effect of clinical variable	Effect of time	Interaction effect time x clinical variable
Presurgical IQ	✓***	x	x
Side of surgery	✓*	x	x
Etiology	(✓)	x	x
Surgery type	x	x	x
Localization	x	x	x
Age at onset	✓*	✓*	✓*
Duration of epilepsy	✓*	x	(✓)
Seizure outcome	x	x	x
ASM load	x	x	x

Note. x = no significant effect; ✓ = significant effect; (✓) = non-significant trend ($p < 0.10$); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

3.4. Analyses of Subgroups with Significant Change

In sum, none of the following analyses of subgroups with significant EF change for different clinical variables, reached significance (p>0.5).

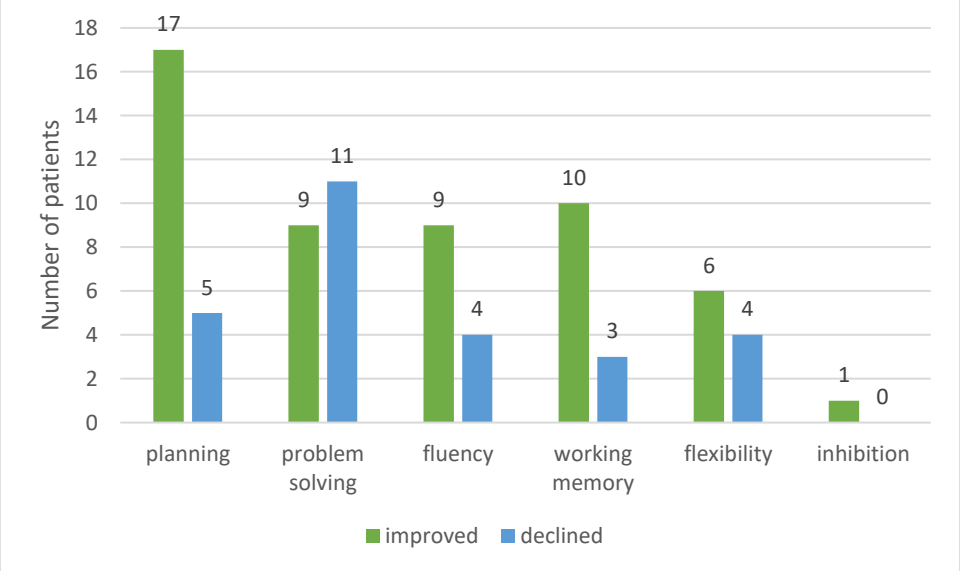

Figure 4 : The number of patients who have shown an improvement or decline from baseline to 2 years post-surgical follow-up of at least one standard deviation.

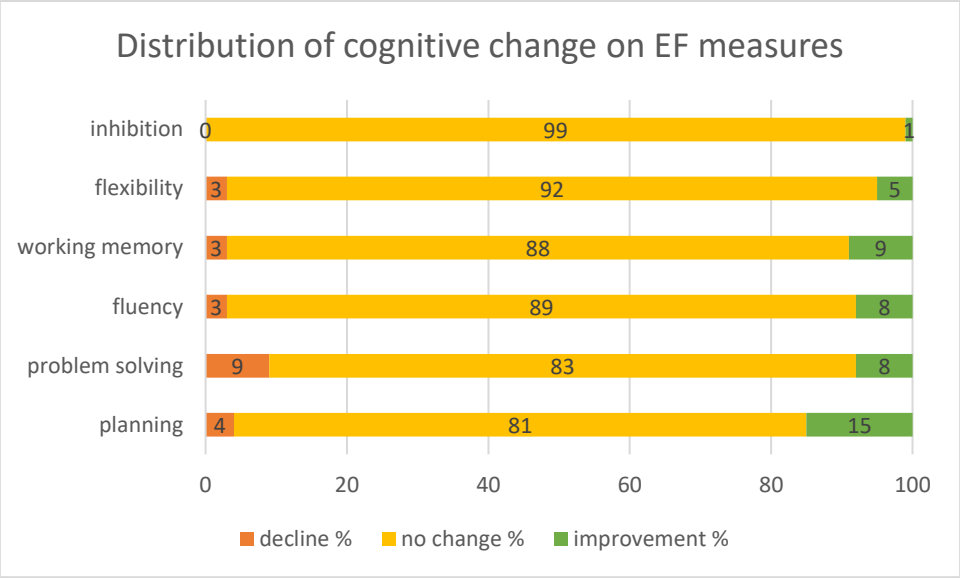

Figure 5 : Distribution of cognitive change (deterioration, no change, improvement) on measures of Executive Functions in percentages.

3.4.1. Analysis of Change in Planning

The variable Change in Planning comprised the two groups 'improved' and 'declined', which referred to patients who either improved or declined by at least 1 standard deviation between the presurgical evaluation and the 24 months postsurgical evaluation in the block design task. From the cohort of 117 patients, 22 patients showed a significant change in Planning ability 2 years after surgery (19%). 17 improved (15%) and 5 declined significantly (4%). The design was therefore unbalanced.

3.4.1.1. IV Presurgical IQ. The presurgical IQ of the increased and the declined group was compared. No outliers were observed in the data, both groups were normally distributed, assessed by the Shapiro-Wilk test (improved p= .39, declined p=.65). Presurgical IQ was lower in the declined group (M = 88.2, SD = 8.7) than in the improved group (M =99.1, SD = 15.8). The Welch test, interpreted because of the unbalanced design, showed a trend towards significance of the difference between presurgical IQs of the improved and the declined group, with mean presurgical IQ 10.9 points (95%-CI[-0.98, 22.7]) lower for the declined group, t(12.6)= 1.99, p=.069. Despite the lack of significance, probably due to small sample size, there was a medium effect size (r =.49).

3.4.1.2. IV Side of Surgery. A Fisher's exact test between the variable Change in Planning with its two groups 'improved' and 'declined' and the variable side of surgery with its two options left and right hemispheric surgery, was used, because of cell frequencies below 5. In the 'improved' group, 9 patients had right hemisphere surgery and 8 patients had left

hemisphere surgery. In the declined group, 5 had surgery on the right side, none on the left side. Results showed no significant association between the two groups and the hemisphere on which surgery was performed, p= .12, φ = 0.41.

3.4.1.3. IV Etiology. A Fisher's exact test between the variable change in Planning with its two groups 'improved' and 'declined' and the variable etiology, which had 2 options 'tumor' and 'other' was used, because of cell frequencies below 5. In the 'improved' group, 9 patients had surgery for a tumor, 8 had other etiologies. In the declined group, 1 patient had a tumor, 4 had other etiologies. Results showed no significant association between the two 'change in Planning' groups and the etiology, p= .32, φ = 0.28.

3.4.1.4. IV Surgery Type. Again, a Fisher's exact test between the variable 'change in Planning' with its two groups 'improved' and 'declined' and the variable surgery type, for which the 2 options 'large' and 'small' was used, because of cell frequencies below 5. In the 'improved' group, 5 patients had large resections and 12 had smaller resections. In the declined group, 1 patient had large resections, 4 had small resections. Results showed no significant association between the two 'change in Planning' groups and the surgery type, p= .99, φ= 0.09.

3.4.1.5. IV Localization. A Fisher's exact test between the change in Planning with its two groups 'improved' and 'declined' and the variable localization, which has 2 options 'frontal' and 'extrafrontal' was used instead of Chi-square-test, because of cell frequencies below 5. In the 'improved' group, 6 patients had frontal, 11 had extrafrontal surgery. In the declined group, 2 had frontal, 3 had extrafrontal surgery. Results showed no significant association between the two groups and the localization of surgery, p= .99, φ= 0.04.

3.4.1.6. IV Age at Onset. Boxplots showed there were no outliers in the data. Both groups were normally distributed, as assessed by the Shapiro-Wilk-test, improved p = .16 and declined p = .28. Age at onset was higher in the improved group (M = 7.3 years , SD = 4.7) than in the declined group (M= 6.5, SD = 5.9). The age at onset was 0.87 years lower for the improved group (95%-CI [-6.24, 7.97]). To report the possible significance of the difference between the two groups, the Welch test was interpreted, because of the unbalanced design. However, there was no statistically significant difference between the improved and the declined group, t(5.59)= 0.30, p=.77, r=0.14.

3.4.1.7. IV Duration of Epilepsy. The improved group was not normally distributed, as assessed by the Shapiro-Wilk test (p =.01). The distributions did not differ between both groups, Kolmorov-Smirnov p = .49, allowing the Mann-Whitney-U-Test to be conducted to determine if there were differences in duration of epilepsy between the two groups. There was no significant difference in duration of epilepsy between the improved (*Mdn* = 2.58) and the declined groups (*Mdn* = 4.75), U = 37.0, Z = -0.43, p=.66, r = 0.092.

3.4.1.8. IV Seizure Outcome. A Fisher's exact test between the variable 'change in Planning' with its two groups 'improved' and 'declined' and the variable Seizure outcome, for which 2 options '1a' and '>1a' were used, because of cell frequencies below 5. '1a' can be referred to as the completely seizure free group, while '>1a' is not seizure free. In the 'improved' group, 10 patients were seizure free and 7 were not. In the declined group, 2 patients were seizure free, 2 were not. Results showed no significant association between the two groups and the Seizure outcome, p= .99, φ = 0.70.

3.4.1.9. IV ASM Load. A Fisher's exact test between the variable 'change in Planning' with its two groups 'improved' and 'declined' and the variable ASM load, for which 2 options '0 ASM' and '≥ 1 ASM' were used, because of cell frequencies below 5. In the 'improved' group, 5 patients discontinued all ASMs and 12 were taking 1 or more ASMs. In the declined group, none took no ASM, 4 were taking 1 or more. Results showed no significant association between the two groups and the ASM load, p= .53, φ = 0.27.

3.4.2. Analysis of Change in Problem Solving

As for the variable Change in Planning, the variable change in Problem Solving comprised the two groups 'improved' and 'declined', which referred to patients who either improved or declined by at least 1 standard deviation between the presurgical evaluation and the 24 months postsurgical evaluation in matrix reasoning. This dependent variable was analyzed in relationship to the same set of independent variables as used for the analyses of change in Planning. From the cohort of 117 patients, 20 patients (17%) showed a significant change in Problem Solving 2 years after surgery. 9 improved (8%) and 11 (9%) declined significantly. The design was therefore balanced.

3.4.2.1. IV Presurgical IQ. The presurgical IQ of the increased and the declined group was compared. No outliers were observed in the data, both groups were normally distributed,

assessed by the Shapiro-Wilk test (improved p = .23, declined p =.61). Homoscedasticity was given as assessed by the Levene test (p = .18). Presurgical IQ was lower in the declined group (M = 94.91, SD = 9.40) than in the improved group (M = 98.11, SD = 14.22).

The unpaired t-test showed no statistically significant difference between presurgical IQs of the improved and the declined group, with mean presurgical IQ 3.2 points (95%-*CI* [-8.4, 14.8]) lower for the declined group, $t(18)$= 0.58, p=.57. Despite the lack of significance, probably due to small sample size, there was a small effect size (r = 0.14).

3.4.2.2. IV Side of Surgery. A Fisher's exact test between the variable Change in Problem Solving with its two groups 'improved' and 'declined' and the variable side of surgery with its two options left and right hemispheric surgery, was used, because of cell frequencies below 5. In the 'improved' group, 5 patients had right hemisphere surgery and 4 patients had left hemisphere surgery. In the declined group, 5 had surgery on the right side, 6 on the left side. Results showed no significant association between the two groups and the hemisphere on which surgery was performed, p= .99, φ = 0.1.

3.4.2.3. IV Etiology. A Fisher's exact test between the variable change in Problem Solving with its two groups 'improved' and 'declined' and the variable etiology, which had 2 options 'tumor' and 'other' was used, because of cell frequencies below 5. In the 'improved' group, 1 patient had surgery for a tumor, 8 had other etiologies. In the declined group, 4 patients had a tumor, 7 had other etiologies. Results showed no significant association between the two 'change in Planning' groups and the etiology, p= .32, φ = 0.29**.**

3.4.2.4. IV Surgery Type. Again, a Fisher's exact test between the variable 'change in Problem Solving' with its two groups 'improved' and 'declined' and the variable surgery type, for which the 2 options 'large' and 'small' was used, because of cell frequencies below 5. In the 'improved' group, 4 patients had large resections and 5 had smaller resections. In the declined group, 5 patients had large resections, 6 had small resections. Results showed no significant association between the two 'change in Planning' groups and the surgery type, p= .99, φ= 0.01.

3.4.2.5. IV Localization. A Fisher's exact test between the change in Problem Solving with its two groups 'improved' and 'declined' and the variable localization, which has 2 options 'frontal' and 'extrafrontal' was used instead of Chi-square-test, because of cell frequencies below 5. In the 'improved' group, 1 patient had frontal, 8 had extrafrontal surgery. In the

declined group, 3 had frontal, 8 had extrafrontal surgery. Results showed no significant association between the two groups and the localization of surgery, p= .59, φ= 0.20.

3.4.2.6. IV Age at Onset. Boxplots showed there were no outliers in the data. Both groups were normally distributed, as assessed by the Shapiro-Wilk-test, improved p = .23 and declined p = .61. Homoscedasticity was given as assessed by the Levene test (p= .69). Age at onset was higher in the improved group (M = 6.7 years , SD = 4.5) than in the declined group (M= 5.9, SD = 3.9). The age at onset was 0.77 years lower for the declined group (95%-*CI* [-3.18, 4.73]). The difference between both groups was not statistically significant, $t(18)$= 0.41, p= .69, r= 0.09.

3.4.2.7. IV Duration of Epilepsy. Both groups were normally distributed, as assessed by the Shapiro-Wilk test (improved p =.49, declined p=.55). Boxplots showed there were no outliers in the data. Duration of epilepsy at the time of surgery was shorter in the improved group (M = 5.12 years, SD = 3.57) than in the declined group (M= 7.40, SD = 5.50). Homoscedasticity was given as assessed by the Levene test (p= .13); The unpaired t-test showed there was no statistically significant difference between the improved and the declined group, with mean age at surgery being 2.28 years (95%-*CI* [-6.73, 2.17]) lower for the improved group, $t(18)$= -1.08, p=.30, r= 0.25.

3.4.2.8. IV Seizure Outcome. A Fisher's exact test between the variable 'change in Problem Solving' with its two groups 'improved' and 'declined' and the variable Seizure outcome, for which 2 options '1a' and '>1a' were used, because of cell frequencies below 5. '1a' can be referred to as the completely seizure free group, while '>1a' is not seizure free. In the 'improved' group, 5 patients were seizure free and 3 were not. In the declined group, 7 patients were seizure free, 4 were not. Results showed no significant association between the two groups and the Seizure outcome, p= .99, φ = 0.01.

3.4.2.9. IV ASM Load. A Fisher's exact test between the variable 'change in Problem Solving' with its two groups 'improved' and 'declined' and the variable ASM load, for which 2 options '0 ASM' and '≥ 1 ASM' were used, because of cell frequencies below 5. In the 'improved' group, 2 patients discontinued all ASMs and 6 were taking 1 or more ASMs. In the declined group, 3 took no ASM, 8 were taking 1 or more. Results showed no significant association between the two groups and the ASM load, p= .99, φ = 0.03.

3.4.3. Analysis of Change in Fluency

As for the previous variable of change, the variable "Change in Fluency" comprised the two groups 'improved' and 'declined', which referred to patients who either improved or declined by at least 1 standard deviation between the presurgical evaluation and the 24 months postsurgical evaluation in phonological Fluency tasks. This dependent variable was analyzed in relationship to the same set of independent variables as used for the previous analyses of change. From the cohort of 117 patients, 13 patients showed a significant change in Fluency 2 years after surgery. 9 improved and 4 declined significantly. The design was therefore imbalanced.

3.4.3.1. IV Presurgical IQ. The presurgical IQ of the increased and the declined group was compared. Two outliers were observed in the data. In addition, the improved group was not normally distributed, as assessed by the Shapiro-Wilk test (improved p= .03, declined p=.74), so a non parametric test was selected. The distributions did not differ between the improved and the declined group, Kolmorov-Smirnov p = .96, allowing the Mann-Whitney-U-Test to be conducted to determine if there were differences in presurgical IQ between the two groups. There was no statistically significant difference in presurgical IQ between the improved (*Mdn* = 104.00) and the declined groups (*Mdn* = 97.00), U = 13.00, Z = -0.77, p=.50, r = 0.008.

3.4.3.2. IV Side of Surgery. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable side of surgery with its two options left and right hemispheric surgery, was used, because of cell frequencies below 5. In the 'improved' group, 5 patients had right hemisphere surgery and 4 patients had left hemisphere surgery. In the declined group, 3 had surgery on the right side, 1 on the left side. Results showed no significant association between the two groups and the hemisphere on which surgery was performed, p= .99, φ = 0.18.

3.4.3.3. IV Etiology. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable etiology, which had 2 options 'tumor' and 'other' was used, because of cell frequencies below 5. In the 'improved' group, 4 patients had surgery for a tumor, 5 had other etiologies. In the declined group, 1 patient had a tumor, 3 had other etiologies. Results showed no significant association between the two 'change in Planning' groups and the etiology, p= .99, φ = 0.18.

3.4.3.4. IV Surgery Type. Again, a Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable surgery type, for which the 2 options 'large' and 'small' was used, because of cell frequencies below 5. In the 'improved' group, 2 patients had large resections and 7 had smaller resections. In the declined group, 1 patient had large resections, 3 had small resections. Results showed no significant association between the two 'change in Fluency' groups and the surgery type, p= .99, φ= 0.03.

3.4.3.5. IV Localization. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable localization, which has 2 options 'frontal' and 'extrafrontal' was used instead of Chi-square-test, because of cell frequencies below 5. In the 'improved' group, 4 patients had frontal, 5 had extrafrontal surgery. In the declined group, none had frontal, 4 had extrafrontal surgery. Results showed no significant association between the two groups and the localization of surgery, p= .23, φ= 0.44.

3.4.3.6. IV Age at Onset. Boxplots showed there were no outliers in the data. Both groups were normally distributed, as assessed by the Shapiro-Wilk-test, improved p = .07 and declined p = .56. Homoscedasticity was given as assessed by the Levene test (p= .86). Age at onset was higher in the declined group (M = 8.0 years, SD = 4.9) than in the improved group (M= 7.8, SD = 3.6). The age at onset was 0.16 years lower for the improved group (95%-*CI* [-5.41, 5.08]). The Welch t-test was interpreted instead of the unpaired t-test because of unbalanced design. The difference between both groups was not statistically significant, t(4.46)= -0.06, p= .96, r= 0.03.

3.4.3.7. IV Duration of Epilepsy. Both groups were normally distributed, as assessed by the Shapiro-Wilk test (improved p =.42, declined p=.96). Boxplots showed there were no outliers in the data. Duration of epilepsy at the time of surgery was longer in the improved group (M = 6.06 years, SD = 4.37) than in the declined group (M= 4.60, SD = 3.17). Homoscedasticity was given as assessed by the Levene test (p= .45); The unpaired t-test was replaced by the Welch t-test because of the unbalanced design. There was no statistically significant difference between the improved and the declined group, with duration of epilepsy being 1.45 years (95%-*CI* [-3.51, 6.42]) longer for the improved group, t(8.05)= 0.67, p=.52, r= 0.23.

3.4.3.8. IV Seizure Outcome. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable Seizure outcome, for which 2 options '1a' and '>1a' were used, because of cell frequencies below 5. '1a' can be referred to as the completely seizure free group, while '>1a' is not seizure free. In the 'improved' group, 7 patients were seizure free and 2 were not. In the declined group, 4 patients were seizure free, 0 were not. Results showed no significant association between the two groups and the Seizure outcome, p= .99, φ = 0.28.

3.4.3.9. IV ASM Load. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable ASM load, for which 2 options '0 ASM' and '≥ 1 ASM' were used, because of cell frequencies below 5. In the 'improved' group, 4 patients discontinued all ASMs and 5 were taking 1 or more ASMs. In the declined group, 3 took no ASM, 1 was taking 1 or more. Results showed no significant association between the two groups and the ASM load, p= .56, φ = 0.28.

3.4.4. Analysis of Change in Working Memory

Again, as for previous variables of change, the variable "Change in Working Memory" comprised two groups, which referred to patients who either improved or declined by at least 1 standard deviation between the presurgical evaluation and the 24 months postsurgical evaluation in the cumulative measure 'Working Memory', which consists of verbal Working Memory tasks. This dependent variable was analyzed in relationship to the same set of independent variables as used for the previous analyses of change. From the cohort of 117 patients, 13 patients showed a significant change in Working Memory 2 years after surgery. 10 improved and 3 declined significantly. The design was therefore unbalanced.

3.4.4.1. IV Presurgical IQ. The presurgical IQ of the increased and the declined group was compared. No outliers were observed in the data. The two groups were normally distributed, as assessed by the Shapiro-Wilk test (improved p= .99, declined p=.69). Homoscedasticity was given as assessed by the Levene test (p= .92). Presurgical IQ was higher in the declined group (M = 94.33 years , SD = 12.66) than in the improved group (M= 89.30, SD = 11.24). The presurgical IQ was 5.03 points lower for the improved group (95%-CI [-30.81, 20.74]). The Welch t-test was interpreted instead of the unpaired t-test because of unbalanced design. The difference between both groups was not statistically significant, t(3.02)= -0.62, p= .58, r= 0.34.

3.4.4.2. IV Side of Surgery. A Fisher's exact test between the variable 'change in Working Memory' with its two groups 'improved' and 'declined' and the variable side of surgery with its two options left and right hemispheric surgery, was used, because of cell frequencies below 5. In the 'improved' group, 4 patients had right hemisphere surgery and 6 patients had left hemisphere surgery. In the declined group, none had surgery on the right side, 3 on the left side. Results showed no significant association between the two groups and the hemisphere on which surgery was performed, p= .50, φ = 0.19.

3.4.4.3. IV Etiology. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable etiology, which had 2 options 'tumor' and 'other' was used, because of cell frequencies below 5. In the 'improved' group, 3 patients had surgery for a tumor, 7 had other etiologies. In the declined group, 1 patient had a tumor, 2 had other etiologies. Results showed no significant association between the two 'change in Planning' groups and the etiology, p= .99, φ = 0.03.

3.4.4.4. IV Surgery Type. Again, a Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable surgery type, for which the 2 options 'large' and 'small' was used, because of cell frequencies below 5. In the 'improved' group, 6 patients had large resections and 4 had smaller resections. In the declined group, 2 patients had large resections, 1 had small resections. Results showed no significant association between the two 'change in Fluency' groups and the surgery type, p= .99, φ= 0.058.

3.4.4.5. IV localization. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable localization, which has 2 options 'frontal' and 'extrafrontal' was used instead of Chi-square-test, because of cell frequencies below 5. In the 'improved' group, 2 patients had frontal, 8 had extrafrontal surgery. In the declined group, none had frontal, 3 had extrafrontal surgery. Results showed no significant association between the two groups and the localization of surgery, p= .99, φ= 0.234

3.4.4.6. IV Age at Onset. Boxplots showed there were no outliers in the data. Both groups were normally distributed, as assessed by the Shapiro-Wilk-test, improved p = .28 and declined p = .93. Homoscedasticity was given as assessed by the Levene test (p= .06). Age at onset was slightly higher in the improved group (M = 7.51 years, SD = 4.35) than in the declined group (M= 7.28, SD = 6.09). The age at onset was 0.23 years higher for the improved group

(95%-*CI* [-12.74, 13.20]). The Welch t-test was interpreted instead of the unpaired t-test because of unbalanced design. The difference between both groups was not statistically significant, $t(2.65) = 0.06$, $p = .96$, $r = 0.038$.

3.4.4.7. IV Duration of Epilepsy. Both groups were normally distributed, as assessed by the Shapiro-Wilk test (improved $p = .44$, declined $p = .73$). Boxplots showed there were no outliers in the data. Duration of epilepsy at the time of surgery was longer in the improved group ($M = 5.75$ years, $SD = 4.37$) than in the declined group ($M = 4.78$, $SD = 4.33$). Homoscedasticity was given as assessed by the Levene test ($p = .34$). The unpaired t-test was replaced by the Welch t-test because of the unbalanced design. There was no statistically significant difference between the improved and the declined group, with duration of epilepsy being 0.97 years (95%-*CI* [-7.63, 9.57]) longer for the improved group, $t(3.33) = 3.40$, $p = .75$, $r = 0.18$.

3.4.4.8. IV Seizure outcome. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable Seizure outcome, for which 2 options '1a' and '>1a' were used, because of cell frequencies below 5. '1a' can be referred to as the completely seizure free group, while '>1a' is not seizure free. In the 'improved' group, 3 patients were seizure free and 7 were not. In the declined group, 2 patients were seizure free, 1 was not. Results showed no significant association between the two groups and the Seizure outcome, $p = .51$, $\varphi = 0.318$.

3.4.4.9. IV ASM load. A Fisher's exact test between the variable 'change in Fluency' with its two groups 'improved' and 'declined' and the variable ASM load, for which 2 options '0 ASM' and '≥ 1 ASM' were used, because of cell frequencies below 5. In the 'improved' group, 4 patients discontinued all ASMs and 6 were taking 1 or more ASMs. In the declined group, 1 took no ASM, 2 were taking 1 or more. Results showed no significant association between the two groups and the ASM load, $p = .99$, $\varphi = 0.58$.

3.4.5. Analysis of Change in Flexibility

The variable "Change in Flexibility" comprised two groups, which referred to patients who either improved or declined by at least 1 standard deviation between the presurgical evaluation and the 24 months postsurgical evaluation in the test measure 'symbol search', from the Wechsler test batteries. As before, this dependent variable was analyzed with the same set

of independent variables as used for the previous analyses of change. From the cohort of 117 patients, 10 patients showed a significant change in Flexibility 2 years after surgery, which represented only 8.5% of the cohort. 6 improved and 4 declined significantly. The design was therefore unbalanced. For continuous variables, the Welch t-test was used instead of the unpaired t- test.

3.4.5.1. IV Presurgical IQ. No outliers were observed in the data when comparing the presurgical IQ of the 'increased' and the 'declined' Flexibility groups. The two groups were normally distributed, as assessed by the Shapiro-Wilk test (improved p= .97, declined p=.42). Homoscedasticity was given as assessed by the Levene test (p=.43). Presurgical is lower in the 'improved' group (M = 95.67, SD = 19.93), than in the 'declined' group (M= 101.50, SD = 11.48). The presurgical IQ was 5.83 IQ points lower for the improved group (95%-*CI* [-28.82, 17.15]). The Welch t-test showed that the difference between both groups was not statistically significant, $t(7.94)$= -0.59, p= .57, r= 0.18.

3.4.5.2. IV Side of Surgery. A Chi-square test between the variable 'change in flexibilty' with its two groups 'improved' and 'declined' and the variable side of surgery with its two options left and right hemispheric surgery, was conducted. In the 'improved' group, 1 patients had right hemisphere surgery and 5 patients had left hemisphere surgery. In the declined group, 2 had surgery on the right side, 2 on the left side. Results showed no significant association between the two groups and the hemisphere on which surgery was performed, p= .50, φ = 0.36.

3.4.5.3. IV Etiology. A Fisher's exact test between the variable 'change in Flexibility' with its two groups 'improved' and 'declined' and the variable etiology, which had 2 options 'tumor' and 'other' was used, because of cell frequencies below 5. 2 patients in the 'improved' group had surgery for a tumor, 4 had other etiologies. In the declined group, only 1 patient had a tumor, and 3 had other etiologies. Results showed no significant association between the two 'change in Flexibility' groups and the etiology, p= .99, φ = 0.09.

3.4.5.4. IV Surgery Type. A Fisher's exact test between the variable 'change in Flexibility' with two groups, 'improved' and 'declined', and the variable 'surgery type' with the two options 'large' and 'small' was conducted. In the 'improved' group, 3 patients had a large surgery and 3 patients had a smaller, tailored surgery. In the declined group, 2 had a large

surgery, whereas also 2 had a small surgery. Results showed no significant association between the two groups and the hemisphere on which surgery was performed, p= .99, $\varphi < 0.01$.

3.4.5.5. IV Localization. A Fisher's exact test between the variable 'change in Flexibility' with its two groups 'improved' and 'declined' and the variable localization, which has 2 options 'frontal' and 'extrafrontal' was used instead of Chi-square-test, because of cell frequencies below 5. In the 'improved' group, 1 patient had frontal, 5 had extrafrontal surgery. In the declined group, 0 had frontal, 4 had extrafrontal surgery. Results showed no significant association between the two groups and the localization of surgery, p= .99, φ= 0.27.

3.4.5.6. IV Age at Onset. Boxplots showed there were no outliers in the data. The Shapiro-Wilk-test showed that the groups were normally distributed, improved p = .44 and declined p = .44. Homoscedasticity was given as assessed by the Levene test (p= .79). Age at onset was slightly higher in the declined group (M = 9.10 years , SD = 4.39) than in the improved group (M= 8.79, SD = 4.61). The age at onset was 0.313 years higher for the declined group (95%-*CI* [-7.20, 658]). The Welch t-test showed no significant difference between both groups, t(6.86)= -0.11, p= .92, r= 0.04.

3.4.5.7. IV Duration of epilepsy. Both groups were normally distributed, as assessed by the Shapiro-Wilk test (improved p =.16, declined p=.74). Boxplots showed there were no outliers in the data. Duration of epilepsy at the time of surgery was shorter in the improved group (M = 4.40 years, SD = 4.25) than in the declined group (M= 4.67, SD = 2.77). Homoscedasticity was given as assessed by the Levene test (p= .25). The Welch t- test showed that there was no statistically significant difference between the improved and the declined group, with duration of epilepsy being 0.28 years (95%-*CI* [-5.39, 4.84]) longer for the declined group, t(7.99)= -0.13, p=.90, r= 0.04.

3.4.5.8. IV Seizure outcome. A Fisher's exact test between the variable 'change in Flexibility' with its two groups 'improved' and 'declined' and the variable 'Seizure outcome' with its two options '1a' and '>1a' was conducted. In the 'improved' group, 3 patients were seizure free '1a' and 2 patients still had seizures ('>1a'). In the declined group, only 1 patient was seizure free, 3 still had seizures. Results showed no significant association between the two groups and the hemisphere on which surgery was performed, p= .57, φ = 0.25.

3.4.5.9. IV ASM load. A Fisher's exact test between the variable 'change in Flexibility' with its two groups 'improved' and 'declined' and the variable ASM load, for which 2 options '0 ASM' and '≥ 1 ASM', were used because of cell frequencies below 5. In the 'improved' group, 2 patients were not taking ASMs and 4 were taking 1 or more ASMs. In the declined group, 1 discontinued all ASMs, 3 were taking 1 or more. Results showed no significant association between the two groups and the ASM load, p= .99, φ = 0.09.

3.4.6. Summary of Subgroups with Significant change in EF

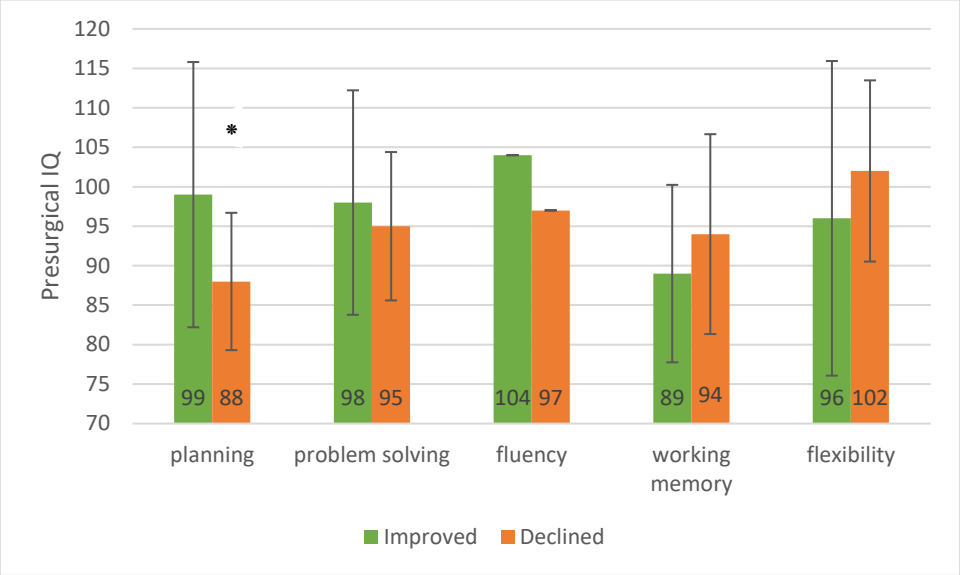

Figure 6 : Mean scores (± standard deviations) of patients at baseline and 2 years follow-up for the variable Presurgical IQ.

Notes. Results of the Welch test for normally distributed samples, and of the Mann-Whitney-U-test for not normally distributed samples in the Fluency test. Due to extreme outliers, no SD is indicated here.

* trend toward significance, p = .069.

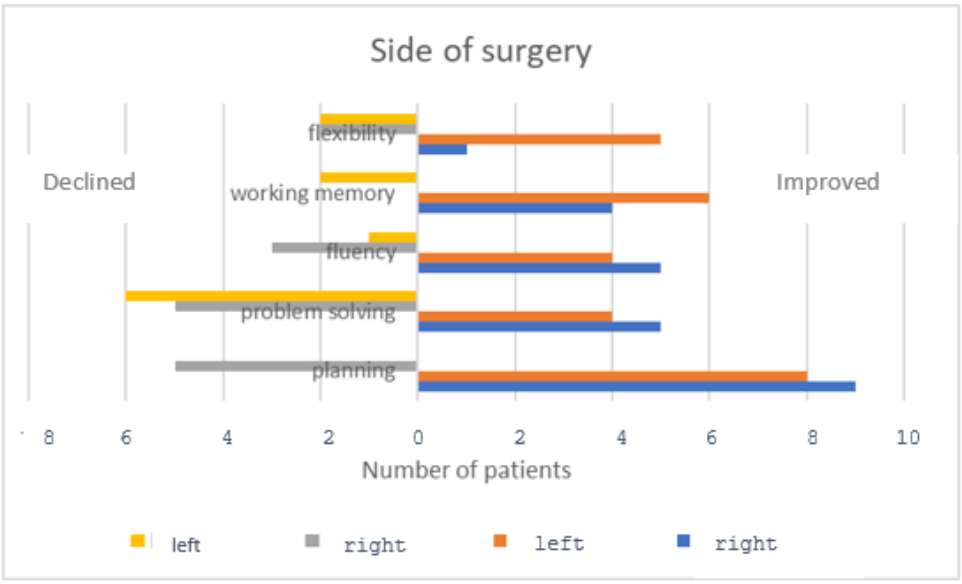

Figure 7 : Patients with left or right hemispheric surgery with significant post-surgical improvement or decline in different executive functions.

4. Discussion

This dissertation focuses on the longitudinal development of executive functions following paediatric epilepsy surgery, a research field that has not yet been thoroughly investigated. The explorative and retrospective analysis of multicentric, longitudinal data of a large cohort of 117 children and adolescents aged between 4 and 18, who underwent epilepsy surgery aimed to shed light onto the following overarching questions. First, which are the developmental pathways for executive functions after paediatric epilepsy surgery? Second, how do different presurgical, surgical and clinical factors impact the development of executive functions? And third, which of these factors are associated with significant executive functions (EF) decline or improvement after paediatric epilepsy surgery?

Different from most neuropsychological outcome studies on paediatric epilepsy surgery, patients with different types of surgical interventions, etiologies and localizations of epilepsy were considered together in this research at hand. First, on a group level EF were not severely impacted in children undergoing epilepsy surgery, neither before nor after surgery, which was unexpected. For almost all evaluated EF, the overall performance was in the lower average. Change over time after surgery, exceeding the expected developmental growth, was only present in a few investigated EF. Even when significant, the extent of change was small. Hence, the impact on daily performance of the concerned children and youth is expected to be minimal. Second, the different clinical factors do not impact the different EF equally. A set of factors, such as age at onset, duration of epilepsy, presurgical IQ and side of surgery seem to have a

more global impact on EF, other factors, such as localization and etiology have a more specific impact on certain EF. When a factor impacts an EF, the difference made on performance is generally small. Third, analyses of subgroups of patients, who either made significant improvement or had an important decline after surgery in EF, do not allow to find predictors for this change. Only a small part of the cohort experienced significant changes in EF after surgery (3% to 15% of the cohort, depending on the task).

In the following, the main findings will be discussed and its implications for theory and practice deduced. Strengths and limitations will be presented and a prospect on future research will be given, before closing with a general conclusion.

4.1. Developmental Pathways of EF After Paediatric Epilepsy Surgery

Cognitive outcome after epilepsy surgery in children has been a growing field of research in the past two decades, especially since epilepsy surgery has become a recognized and widespread therapy method for refractory epilepsy in this age group. Research up to date has mainly focused on intellectual outcome in paediatric patients, for one because extensive data could be gathered since most of the studies are retrospective and IQ test batteries usually represent the heart of the neuropsychological evaluation in children (Baxendale et al., 2016). Second, IQ test batteries offer the advantage of an aggregated measure of different cognitive abilities such as certain aspects of language, of EF and of visuo-spatial skills (Flanagan et al., 2013). Further it is one of the most ecologically valid psychometric measures and is a strong predictor for academic achievement and psychosocial development (Helmstaedter et al., 2019). Studies on specific cognitive functions have been mainly focused on memory and language outcomes in surgical subgroups, such as temporal and frontal lobe surgery patients or tumor patients (Baldeweg & Skirrow, 2015; Ramantani & Reuner, 2018; Ramantani et al., 2014). The dissertation at hand is the first investigation to the best of our knowledge, focused on executive functions in a large surgical paediatric cohort, furthermore in a longitudinal manner, up to 5 years after surgery. The ultimate purpose of EF is to allow adapted behaviour when no preestablished schema of action is available (e.g. Lezak, 1982). EF are key competencies for academic achievements and adaptive social functioning, they support other cognitive functions like memory and visuospatial reasoning and therefore need more consideration in the context of paediatric epilepsy surgery (Zelazo & Carlson, 2020; Puka & Smith, 2017). Very sparse literature exists on EF in this context to propose hypotheses for the different developmental pathways for specific executive functions, which is why an explorative study design was decided to be most appropriate.

Our cohort was comparable to other paediatric epilepsy surgery cohorts in age at onset, duration of epilepsy, gender distribution, localization of surgery and etiology (Ramantani & Reuner, 2017; Smith & Baldeweg, 2017). Postsurgical seizure control was also comparable, and the long-term outcome was especially positive: 6 months after surgery, 72% of patients were completely seizure free (Engel 1a). After 5 years, 65% of patients were still in the Engel 1a category, only 2% reported no worthwhile improvement since surgery. Regarding Antiseizure medication (ASM) load, before surgery most patients took 2 (51%), 1 (27%) or 3 (17%) ASM. 6 and 12 months after surgery more patients took only one ASM (53%; 56%), less took 2 ASM (43%; 31%), only very few had discontinued ASM (1%; 6%). At 24 and 60 months after surgery, ASM intake was reduced and similar for both evaluation times: about ¼ of the cohort had discontinued ASM (25%; 24%). Most patients still took 1 ASM (46%; 46%), and about a third took 2 ASM (27%; 30%). Despite very good rates of seizure freedom after surgery, half as many patients in our cohort were ASM free 5 years after surgery than in an international, multicenter cohort, in which 54% had completely discontinued ASM 5 years after surgery (Boshuisen et al., 2012). This reflects a more cautious approach to ASM withdrawal in our German multicentre cohort. Furthermore, ASM use was only weakly to moderately linked to seizure outcome at all post-surgical evaluations, except at 6 months after surgery, which is not surprising because in both study centres, the earliest drug withdrawal in seizure free patients is usually after the 6 months postsurgical evaluation.

In the present study, the pathways of the investigated EF on a group level over the course of 5 years after epilepsy surgery were not all taking the same developmental direction. Univariate Multilevel model analyses revealed different developmental patterns: None of the investigated EF, namely Working Memory, Inhibition, Monitoring, Flexibility, Planning, Problem Solving and Fluency, presented a lasting postsurgical decline. Working Memory (Wechsler Working Memory Index and Digit Span) and Planning ability improved over time. When comparing Working Memory performances 6 months and 1 year after surgery, the increase was not sufficient to become significant. For the Wechsler Working Memory index, performance even dropped at the 6 months postsurgical evaluation, before returning to presurgical level 1 year after surgery. 2 years after surgery the continuous increase for both tasks became significant and performance continued to increase until the last evaluation, 5 years after surgery. In other studies, no significant change 6 months to 1 year after surgery has also been described (Lendt et al., 2002). Rizzi and colleagues also found a long-term increase of Working Memory after a mean follow-up of 6 years post-epilepsy surgery (2019).

Further in the present study, Fluency increased significantly right after surgery. Other studies have also found an increase shortly after surgery (Sherman et al., 2011; Garcia-Fernandez et al., 2011), while others did not (Vega et al., 2015; Blanchette & Smith, 2002).

In the study at hand, none of the measures for Inhibition (Go No Go task and D2-KL) showed a significant change in performance. However explorative analyses on the D2-KL task showed tendencies towards significance with increasing performance over time.

The higher order EF, Problem Solving and Monitoring did not show change over time, neither did Flexibility (TMT B and Symbol Search). Explorative analysis of the Flexibility measure TMT B revealed a slow decrease in performance after surgery, which became significant at 24 months after surgery and an increase, back to the presurgical level at 60 months after surgery. This is a similar developmental pattern of an initial postsurgical drop in performance and an increase in the long run as in Working Memory, however not reaching significance, probably due to a smaller sample size. Recovery in cognitive functions after initial declines has also been described for IQ and memory functions before (Gleissner et al., 2005, Puka et al., 2017, Puka and Smith, 2016, Skirrow et al., 2011, 2015).

Declines in the short-term after surgery may be explained by resection of functional brain tissue that harboured cognitive function, supporting the `functional adequacy hypothesis´ (Chelune, 1995) as well as the cognitive decline mechanisms proposed by Moosa and Wyllie (2017). In the present study, for both tasks presenting a postsurgical drop (Wechsler Working Memory index and Trail Making Test B), performance increased in the years afterwards. The cognitive recovery might be due to plasticity and/or to compensatory processes, as it has been shown for learning, data acquisition and for IQ after epilepsy surgery in paediatric patients and young adults (Helmstaedter & Elger, 1998; Skirrow et al., 2011). A slow, functional release of reserve capacities, inhibited by epilepsy before surgery, and enabling further development, is also possible (Moosa & Wyllie, 2017).

On the other hand, Fluency improved right after surgery. Following the improvement mechanisms proposed by Moosa and Wyllie (2017), in this case the dysfunction owing to epilepsy before surgery might have extended outside the surgical resection site and the surgery led to “release” of reserve capacities which were suppressed or disrupted by epilepsy. This gain can also correspond to the `functional reserve model´ by Chelune (1995), in which the unoperated side shows good presurgical functioning and takes over the functions of the operated site. However, due to the heterogeneous surgical cohort in this study, one cannot estimate if the function has been taken over by the contralateral, homologous region of the brain or by a perilesional reorganization around the surgical resection site (Lidzba et al., 2019).

It is not surprising, that all the evaluated EF do not show the same developmental pathway, since EF is an umbrella term, comprising cognitive abilities such as inhibitory control, Working Memory and mental Flexibility (Helmstaedter et al., 2019; Operto et al., 2020). Following Diamond´s EF model (2013; 2020), from these basic EF, higher order EF are built such as Problem Solving, Planning, and reasoning. All these EF are related to each other but distinct at the same time: In their studies founding their unity and diversity model of EF, Friedman and Miyake (2017) demonstrated the correlation between EF as well as the distinction between those. Supporting these findings, neuroimaging studies have shown a common brain network for the different components of EF, a fronto-cingulo-parietal network called the Control network (Udin, 2019). However, specific cortical network activations for the different subcompounds of EF have also been found (Niendam et al., 2012). The different pathways taken by the EF in this study might be related to distinct underlying neural substrates (e.g. differences in structure or network).

For simplicity and comprehensive reasons, the EF tasks in this study were classified by single cognitive constructs, even though every neuropsychological task is impure and taps into different EF and even non-EF cognitive processes (Packwood et al., 2011; Diamond, 2020; Miyake et al., 2000; Friedman & Miyake, 2004). For instance, the test `symbol search´ used in this study to represent mental Flexibility has also been shown to implicate Working Memory as well as visual scanning and psychomotor speed (Kadish et al., 2013). In future studies it will be important to consider the impact of other factors that might explain changes in EF tasks such as attention, language, memory, or visual processing.

Regarding the evolution of the mean scores of EF tasks, which improved over time, changes were minimal, varying less than 1 standard deviation in the present study. This has been described in other paediatric epilepsy surgery studies for other cognitive domains such as language (Puka & Smith, 2016) and memory (Chieffo et al., 2011; Garcia-Fernandez et al., 2011). The mean scores for these EF tasks were all in the lower average before surgery and improved towards the mean over the course of 5 years after surgery. The statistical tendency of low scores to regress towards the mean during subsequent testing sessions cannot be ruled out here, as the multilevel models do not account for this phenomenon (Bland & Altmann, 1994). However, this significant improvement towards the average ability level was not observed for all EF tasks, so gains may more likely reflect sustainability or even acceleration or a small “restart” of cognitive development after developmental regression or stagnation, as it has also been shown for small IQ gains after epilepsy surgery (Schmidlechner et al., 2023, Puka & Smith, 2016).

After the analysis of the different EF pathways for the whole surgical cohort, possible predictors of EF development in this study will be discussed in the context of prior research and theoretical background on EF.

4.2. Influence of Clinical Factors and Time on Long-Term Post-Surgical Development of EF

Presurgical, surgical and postsurgical factors were analysed for our cohort in multivariate Multilevel models. The factor `time´ was always paired with a clinical factor to observe how both factors impacted the different EF in their development before surgery up to 5 years after surgery. Potential predictors of EF development, identified in the research literature, were presurgical IQ, side of surgery, etiology, surgery type, surgical localization, age at onset of epilepsy, duration of epilepsy before surgery, postsurgical seizure outcome and ASM load.

4.2.1. Presurgical IQ

A robust predictor of postsurgical intellectual development is presurgical IQ, as it has been shown in many studies (Ramantani & Reuner, 2017; D´Argenzio et al., 2011; Kaur et al., 2022; Helmstaedter et al., 2020). In general, the higher the presurgical IQ, the higher is the IQ after surgery. Besides a higher postsurgical IQ, a higher presurgical IQ is also predictive of a better postsurgical memory outcome and is supposed to be a marker for structural integrity (Helmstaedter et al., 2020; Puka et al., 2017; Martin et al., 2016). This study at hand showed that this positive influence of a higher IQ on cognitive outcome could be expanded to EF: The higher the presurgical IQ, the more improvement was observed in EF in the postsurgical outcome, mostly independent of time passing after surgery. In fact, there was no significant evolution to be seen between the presurgical and the follow up evaluations for Planning, Problem Solving, Working Memory, Flexibility and Inhibition. A significant interaction effect time x presurgical IQ was observed for Fluency. The regression coefficient 6 months after surgery showed, that a higher presurgical IQ predicted higher postsurgical Fluency. The regression coefficient then regressed minimally at 12 months after surgery, to improve again at 60 months after surgery. However, changes were very small, varying between increases of 0,03 to 0,05 points in z-scores per IQ point.

A strong correlation between IQ and EF has been shown in different studies, for instance IQ and Working Memory (Friedman et al., 2006; Fukuda et al., 2010). The largely used Wechsler IQ test batteries include Working Memory as one of 5 indexes used to evaluate the

general IQ (Petermann, 2017). Diamond even postulates in her EF theory that the higher order EF Problem Solving is equivalent with the concept of fluid intelligence, which is an important factor in most IQ test batteries (Diamond, 2013; Roca et al., 2010). Therefore, it is not surprising that the presurgical IQ level predicts the postsurgical EF functioning.

4.2.2. Side of Surgery

The hemisphere on which surgery is performed is also a possible predictor of postsurgical cognitive outcome. Many studies with a focus on language and memory outcome have investigated the effect of the surgical side on cognition. Results in the paediatric epilepsy surgery population remain inconclusive: In some studies, patients with typical left sided language dominance, verbal capacities including verbal memory are lower and show postsurgical decline more often when the surgery is on the left hemisphere (Garcia-Fernandez et al., 2011), whereas patients with right sided surgery have more deficits in in visuospatial tasks, including visual memory (Jambaqué et al., 2007; Gleissner et al., 2005, Vega et al., 2015, de Koning et al., 2009). However, other studies have found no negative effect of side of surgery on cognitive functions, but a contralateral increase in cognitive functions after surgery (Skirrow et al., 2015; Chieffo et al., 2011). We are unaware of any studies that have compared outcome of EF after right or left hemisphere epilepsy surgery. Neuroimaging studies have revealed left-right hemispheric dissociation of verbal and visuospatial Working Memory in adolescents with activation in the frontal and parietal lobes (Wager & Smith, 2003; Nagel et al., 2013), and right lateralized activation in Monitoring tasks independent of whether the presentation modus was spatial, verbal or temporal (Ambrosini et al., 2020). Activations were more widespread in youth than in adults (Nagel et al., 2013). Fluency tasks can be differentiated in verbal and visual Fluency tasks. Verbal Fluency, as evaluated through phonemic Fluency, activates left frontal areas and subcortical regions, whereas visual Fluency, as evaluated through design Fluency, activates the right frontal and parietal area (Rabinovici et al., 2015; Cipolotti et al., 2021). Inhibition tasks show a bilateral but stronger right fronto-parietal activation, shifting/Flexibility tasks have also a bilateral but stronger left fronto-parietal activation (Rodriguez-Nieto et al., 2022). In the study at hand, an advantage for patients who had undergone left hemispheric surgery was obvious: Left side of surgery was a significant predictor of better postsurgical EF in four out of six analyzed EF. For the EF Flexibility, patients with surgery on the left hemisphere showed a greater increase over time, especially between 12 and 24 months after surgery, than the patients who had right hemispheric epilepsy surgery. For Problem Solving, side of surgery was also a significant factor, however the left surgical group showed a tendency

towards significance with better Problem Solving abilities already before surgery and maintained that difference over time. None of both surgical groups showed a significant change in performance over time. For Fluency, the left and right hemispheric surgery group started off in the lower average. Both groups increased over time, however the right hemispheric group stagnated after 12 months, whereas the left hemispheric group continued to show increased Fluency until the last evaluation 5 years after surgery. Regarding Working Memory, which was evaluated using only verbal Working Memory tasks, the developmental pathway over time was similar: the left and right hemispheric surgery groups started off in the lower average. The left group showed increased performance over time, significantly between 6 and 12 months after surgery, and starting at the 12 months postsurgical evaluation, the difference between the left and right hemispheric surgery groups became significant. These results are unexpected, especially because Working Memory and Fluency were two verbal EF tasks. Regarding previous results on surgical outcome of verbal tasks, left- and right-surgical groups were expected either to remain stable or to progress equally. If one group was expected to show an increase, it was the group who underwent right hemispheric surgery.

As language lateralization data, such as results from WADA tests or fMRI was not available for all patients, it was not control for it in the present study. Therefore, it cannot be excluded that a considerable part of the surgical cohort had atypical language lateralization. In paediatric epilepsy patients, atypical representation of language is not uncommon: Helmstaedter and colleagues estimated 40% to show an atypical language brain activation, and he showed that atypical lateralization of language can even change after epilepsy surgery, in some cases even in adulthood (2006). It is possible that atypical language lateralization had an influence on the Working Memory and Fluency outcomes. There is another reorganizational process which could explain these results: Paediatric patients activate a larger hemispheric network for executive processes than adults, therefore compensatory processes are possible (Nagel et al., 2013; Vogan et al., 2016). Improvements after surgery in the left hemisphere may be due to functional release effects and reorganization within the surgical hemisphere after resection of the epileptogenic zone, as proposed by Moosa and Wyllie (2017). Postsurgical decline would be expected if eloquent function was located in the epileptogenic zone, which is avoided as much as possible through thorough presurgical evaluation and should therefore be rare in our cohort. Further, for the Working Memory and the Fluency task, its ability should be based on the integrity of left frontal and parietal cortex. Cases with interventions in these areas represented only about 35% of left-sided surgical procedures and 16% of our surgical cohort: 15 patients with frontal lobe surgery and 4 patients with parietal lobe surgery out of 53 left-

sided surgical patients from our cohort of 117 patients. In the context of paediatric epilepsy, reorganizational plastic processes in these patients could be expected to have happened before surgery.

Why patients with right hemispheric lesions do not show better verbal EF performance before surgery compared to patients with left sided lesions remains unclear, but crowding effects in the left hemisphere could play a role (Lidzba et al., 2019; Danguecan & Smith, 2019). Regarding the nonverbal task Flexibility, neuroimaging studies have proposed Flexibility to function within a network of prefrontal cortex, the anterior cingulate cortex, and the basal ganglia (Zink et al., 2021). However, the answer to the improvement of the Flexibility measure over time in left hemispheric surgical patients may lie in the task impurity: Flexibility was measured using the Symbol Search test from the Wechsler test batteries, a task which necessitates Flexibility as well as visual scanning and psychomotor speed. Especially visuospatial abilities are typically supported by the right hemisphere (Quin-Conroy et al., 2024). Therefore, improvement in Flexibility can be due to "release" and restart of development after the stop of disturbing, generalized seizure activity in the contralateral brain hemisphere since surgery for left-sided surgery patients, as described in the adapted functional reserve model (Kaur et al., 2022). Improvement in Problem Solving may result from the same brain plasticity mechanisms, because the task is based on visual material (different type of matrices). Problem Solving is based on a broad network of fronto-cingulo-limbic-parietal regions, but unique circuits depending on the verbal or nonverbal nature of the problem have been described, supporting our thesis (Bartley et al., 2018).

4.2.3. Etiology

In our study at hand, etiology was a significant factor modulating EF development for half of the investigated EF. The etiology, the underlying cause of epilepsy, predicted some differences in EF. Time passing since surgery did not significantly change the developmental course of EF, however explorative post hoc analyses showed that changes over time became evident in certain subgroups, which will be described below. Problem Solving, Fluency and Working Memory were impacted by etiology.

For Problem Solving, the mesiotemporal sclerosis group started off with low scores, significantly lower than the mean of the cohort, which was situated in the average performance level. However, over the course of time, this subgroup significantly increased its performance to reach the mean. On the other hand, the group with malformations of cortical development (MCD) was in the average range and mean of the group before surgery and 6 months after

surgery, but showed a steady decrease in performance after that, most probably reflecting a deceleration of development. Other etiological subgroups did not differ significantly from the mean of the group, over time. Regarding Fluency, etiology was a significant predictor of EF, whereas time showed a tendency towards significance. The overall performance was in the lower average, the tumor group was the only group to show significant changes over time regarding the 5 evaluation times. Explorative post hoc analyses revealed other significant results: At the presurgical evaluation time, the gliosis group showed significantly higher performances than the mean. 6 months after surgery, the MCD and the vascular malformation groups, already performing poorly before surgery, differed significantly from the cohort with performances below the mean. However, starting at 12 months, their performance did increase non-significantly, so that it did not differ from the cohort anymore. At 12 and 24 months after surgery, the tumor group showed significant increases and significantly higher performances than the rest of the cohort. At 60 months after surgery, only the dual pathology group was below the mean but 2 etiological subgroups were not represented at that evaluation time (gliosis and vascular malformation). The third EF for which etiology is a predictor, is Working Memory. The MCD group performed significantly below the mean of the cohort before, 6 months and one year after surgery, however it increased its Working Memory ability significantly between the presurgical and the 2 years post-surgical evaluation. The tumor group also increased its Working Memory ability between the presurgical and the 1 year post-surgical evaluation, but always stayed within the mean of the cohort. At the one and two years post-surgical evaluation, the mesiotemporal sclerosis group performed significantly above the mean of the group, in the higher average range. Five years after surgery, none of the groups differed significantly, however as before in Fluency and Problem Solving, 2 etiological groups were missing. Etiology for the EF Flexibility showed a tendency towards significance, but 3 subgroups were missing all together, so an interpretation does not seem appropriate. Many subgroups were also missing for the EF Inhibition. For Planning, neither etiology nor time were significant predictors of EF development, however explorative post-hoc analyses revealed a significant increase in performance between the presurgical and the 5 years post-surgical evaluation for the tumor group.

Our results may have been impacted by small sample sizes in etiological subgroups, with postsurgical evaluations in which whole subgroups were missing, such as vascular malformations, mesio-temporal sclerosis and gliosis groups, or were only represented by less than 10 patients each. This lack of data concerned all postsurgical evaluation times, but more specifically the 5 years post-surgical evaluation. This has probably contributed to differing

results from one EF and from one evaluation time to another, making the interpretation of results difficult. However, there seems to be a tendency for tumor patients to be at least in the mean of the cohort at all evaluation times, mostly at average level and to show progress more consistently over time than other subgroups. Deficits in EF for tumor patients on a group level were not found, which is contrary to results in other studies (Vogt et al., 2018; Mann et al., 2022). The mesiotemporal sclerosis subgroup either showed a significant postsurgical increase or was above the group mean at postsurgical evaluations. Both subgroups have more localized lesions than other etiological groups, which show larger "network" lesions, for instance MCD which can modulate the whole brain network and show more marked cognitive difficulties (Hong et al., 2019; Bast, 2006; Varseema et al., 2019). Therefore, removal of the disturbing, lesional site through surgery can enable functional release mechanisms over time and lead to improvement (Moosa & Willey et al., 2017). In comparison MCD groups and vascular subgroups showed either a decrease in performance or a much slower increase and lower group means for the different EF tasks, reflecting the larger impact of these lesions on neural networks.

4.2.4. Surgery Type

In our study, the surgery type has shown almost no significant effect on the development of EF after paediatric epilepsy surgery, as in other studies in this population on other cognitive functions (Sherman et al., 2012). The only significant results were the following: Planning and Working Memory showed a tendency towards significance for the surgery type, Working Memory also had a tendency towards significance for time, Fluency had a significant effect of time. Explorative post-hoc analysis despite non-significant main results were performed and will be presented below.

For Planning, the intralobar tailored resection group showed significantly lower performances before surgery than the rest of the cohort. Most intralobar tailored resections were in the frontal lobe, since all surgical interventions in the temporal lobe were classified in other, specific categories. Therefore, difficulties in Planning might be due to disturbances before surgery in the fronto-parietal cognitive control network (Niendam et al., 2012). Post-hoc analyses showed that this group improved over time after surgery. For Working Memory, the subgroup intralobar tailored resection is also below the mean of the group after surgery, whereas the AHE group is significantly above the mean of the group at 24 months after surgery, and in the higher mean at all evaluation times. As in Planning, fronto-parietal networks are responsible for Working Memory (Vigneau et al., 2011; Nagel et al., 2013), which might have been more impacted in the intralobar subgroup in this study, and less disturbed in the AHE group, which

had localized surgery in the mesial temporal lobe. For Fluency, time shows a significant effect: the lesionectomy group, the temporal tailored + AHE as well as the standard temporal resection ± AHE significantly increased afters surgery over time, so a large part of the surgical cohort showed improvement in Fluency after surgery, as Sherman and colleagues also found (2011). As for the etiology analyses, subgroups are missing for Fluency and for Flexibility, at the 5 years after surgery evaluation, which make interpretation of results difficult. For the EF Problem Solving, neither time nor surgical type were significant predictors for EF performance, however explorative post-hoc analyses showed a significant and steady improvement after surgery only for the AHE group. For the EF Inhibition, despite non-significant main effects, explorative post-hoc analyses revealed, that patients undergoing multilobar surgeries showed performances which were significantly lower than the cohort after surgery, all the way to 5 years after surgery. Larger resections impact the EF Inhibition right after surgery and do not show improvement over time, plasticity processes seem reduced after large surgical interventions. Surprisingly, other EF were not subject to this phenomenon and mulitlobar resections remained in the mean of the cohort. Other studies also found a tendency towards stability for mulitlobar resections in the long run after surgery (Limpo et al., 2023). A selection bias, the exclusion of patients with intellectual disability, might be impacting these results, as these patients more often present multilobar resections (Limpo et al., 2023).

4.2.5. Localization:

In this study at hand, the factors time and localization of surgery were significantly impacting the EF Planning. For the EFs Problem Solving and Inhibition, only the localization of epilepsy surgery was a modulating factor. Other EF did not have significant main effects, but explorative post-hoc analyses revealed a few differences between subgroups which will be presented below.

For the EF Planning, the main effect time was significant despite the lack of significant variations in time for each localization subgroup. The mean performance of the surgical cohort remained in the average range over time without much variation. However, the frontal subgroup improved between the presurgical workup and the evaluation 2 years after surgery. Further, the main effect localization was significant: The frontal subgroup was performing significantly lower than the mean, 12 months after surgery. Other significant differences between subgroups could not be found. In conclusion, the EF Planning seemed to be particularly impacted in patients with frontal surgery. The EF Problem Solving, on the other hand, was significantly impacted in the parietal group, especially 1 to 5 years after surgery, with significantly lower

results than the rest of the cohort. The EF Inhibition also had a significant main effect of localization. Various localization subgroups stood out at some evaluation time, the parietal subgroup more than others. At the 6 months postsurgical evaluation, the temporal subgroup was more performant than the rest of the cohort, at 12 months after surgery it was the parietal group, whereas the multilobar group showed reduced abilities compared to the cohort. At 24 months after surgery, no localization subgroup differed significantly and at 60 months after surgery, it was again the parietal subgroup which showed Inhibition performances higher than the mean of the group and the multilobar group showed significantly lower Inhibition performance. The EF Fluency did not present significant main effects, but explorative analysis showed that for the frontal group, after an initial performance below the mean before and right after surgery, a significant improvement was noted up to 60 months after surgery, replicating the results obtained in a study by Chieffo et al. (2011). The temporal group, within the mean performance of the cohort before surgery, steadily improved its performance up to 60 months after surgery. For the EF Working Memory, despite lacking significant main effects, explorative analysis showed a drop with performances lower than the mean of the cohort right after surgery for the frontal group, which improved steadily afterwards to reach average level at the 60 months postsurgical evaluation. Esteso-Orduna and colleagues (2021) also found a paediatric FLE group to have more deficits in Working Memory than a TLE group. For the Flexibility task, the mean performances of the different subgroups were in the normative average, and even in explorative analyses, no subgroup differed significantly from the cohort or showed significant variations with time.

Interestingly, both localization subgroups which stand out in the EF analyses are the frontal and the parietal subgroups: For the EF Planning, Fluency and Working Memory, the frontal subgroup showed lower performances than the mean of the cohort 6-12 months after surgery, followed by a slow and steady improvement, usually reaching mean level at 24-60 months after surgery. For the EF Problem Solving, the parietal subgroup also showed a developmental pathway with lower performances than the cohort but a slow and steady improvement over time. Deficits in Problem Solving in a paediatric, surgical parietal lobe epilepsy cohort were also found by Gleissner and colleagues (2008). For the EF Inhibition, the parietal subgroup did not only improve steadily over time as well as showed performances above the mean of the cohort after surgery. Neuroimaging studies have shown a specific fronto-(cingulo)-parietal activation for EF tasks (Niendam et al., 2012; Miller & Cohen, 2001; Na Young Kim et al., 2017). Surgery on these critical areas for EF is expected to lead to impairments. Only in one of the 3 EFs, performance was already below cohort level before

surgery, as expected in malfunction and irritation through epileptic activity of the frontal lobes before surgery. Two other EF showed average performances before surgery, speaking for functional tissue located in the epileptogenic zone, which was then taken away during surgery, leading to a postsurgical decline. However, through plasticity, possibly through contralateral "takeover", the EF could regain its function and restart the development, which takes then 24 to 60 months to reach the mean of the surgical cohort.

Regarding improvement of Fluency in the TLE group, our results did not match those from previous studies: Gleissner and colleagues (2005), as well as Vega and colleagues (2015) did not find significant improvement in Fluency in paediatric temporal lobe epilepsy surgery 12 months after surgery. This present study showed steady growth of Fluency performance in this group, starting 6 months after surgery with already significantly increased Fluency performance.

4.2.6. Age at Epilepsy Onset

In the present study, regression coefficients showed that higher age at epilepsy onset was predictive of higher scores at perisurgical neuropsychological examinations for all evaluated EF tasks. For Planning, the interaction effect time x age at onset was significant: already before surgery, the older the patients were at seizure onset, the better was the Planning ability. This effect of age at onset even increased over time, with even higher scores in Planning. The interaction effect time x age at onset was also significant for the EF task Flexibility. For the other EF tasks, respectively Problem Solving, Fluency, Working Memory and Inhibition, age was also significant. However, the factor time, by itself, did not have a significant influence on the performance.

Age at epilepsy onset has been extensively investigated as a potential predictor of cognitive function in paediatric epilepsy surgery in various studies (Ramantani & Reuner, 2018; Smith & Baldeweg, 2017). To our best knowledge, the effect of age at epilepsy onset on different EF has not been looked at yet. In this study at hand, the protective effect of older age at onset speaks for a hindrance of adequate EF development during sensitive phases of brain development due to epilepsy. Further, our study results indicate that surgery seems unable to repair the damage done, due to epileptic activity at early developmental stages and/or cannot balance the negative effect of the abnormal neural substrate in the brain. If balancing out was possible, the effect of age at surgery would have diminished over time, however it did not. It is still a subject of debate, whether an early age at epilepsy onset has a negative effect on cognition

because seizures themselves impact the cognitive development of an immature brain, or if the underlying brain lesion or dysfunction, which causes seizures early in life, hinders an adequate cognitive development. It is reported that a young age at onset causes circumscribed cognitive dysfunction in verbal memory, independent of epilepsy duration (Ramantani & Reuner, 2018). Other studies report that younger age at seizure onset is related to more widespread lesions and to more global cognitive deficits (Puka et al., 2016a). Lesion extent is also a risk factors for intellectual disability in a recent study by Stefanos-Yakoub and colleagues (2023). Lesion extent has not been a significant predictor of cognition in this study, patients with multilobar resections did not do worse than other surgical and etiological subgroups on most EF tasks. However, patients with hemispherectomies, who usually have very large hemispheric lesions, and patients with intellectual disability have been excluded from the present study.

Cognitive deficits, especially in EF and attention, have been found in paediatric patients at epilepsy onset, before ASM treatment, which supports the hypothesis of an underlying defective neural substrate already existing before epilepsy onset (Reuner et al., 2016). Further, it is possible that duration of seizures, more than the age at onset, is a major etiological factor contributing to the cognitive deficits seen in epilepsy (Puka & Smith, 2016): For instance, Stefano-Yakoub and colleagues (2023) did not find a significant effect of age at onset on IQ in paediatric focal epilepsy patients, but an effect of seizure duration. Duration of epilepsy will be discussed in the next chapter.

4.2.7. Duration of Epilepsy

Duration of epilepsy is a very important possible predictor of outcome in paediatric epilepsy surgery studies because it is one of the only modifiable predictors. Shorter duration of epilepsy until surgery has been linked to a better cognitive outcome in several studies (Kadish et al., 2019; Chieffo et al., 2011; Englot et al., 2013; Gleissner et al., 2005). Vendrame and colleagues (2009) postulate that long-term epilepsy leads to reduced brain plasticity, emphasizing the importance of early intervention. Helmstaedter and Elger (1998) showed that brain plasticity after temporal lobe epilepsy surgery diminishes with age, and that children showed less impacted memory performances after surgery than adolescents did, emphasizing the importance of an early surgical intervention and therefore shorter duration of epilepsy. Gleissner and colleagues also showed that children and adolescents had better compensational capacities after surgery than adults (2005).

To the best of our knowledge, the impact of duration of epilepsy on executive functions has not been investigated yet. In this present study, there was a significant effect of duration of

epilepsy prior to surgery for almost all investigated EF. The EF Planning showed only a tendency towards significance for epilepsy duration. The longer the duration of epilepsy prior to surgery was, the more impacted were the EF. As for the predictor age at epilepsy onset, the effect of time was not significant, meaning that there was no significant change in performance over time after surgery. Patients with longer epilepsy duration were already less performing in EF before surgery and the negative effect of longer seizure duration prior to surgery did not diminish in the years after surgery. This result is also emphasizing the need for an early surgical intervention, as the negative effect of epilepsy duration cannot be overturned by surgery and time. The same conclusion has been drawn by Ramantani and colleagues (2014), as they found that a longer epilepsy duration was linked to a lower pre- and postsurgical IQ, irrespective of the age at onset of epilepsy. These results suggest that an early interruption of diffuse epileptiform discharges coming from a focal lesion can lead to a better outcome of IQ and EF. It might also be possible that the negative impact of longer epilepsy duration in the present study is due to a phenomenon called "growing into deficit" (Moosa & Willie, 2017): Longer duration of epilepsy is usually linked to a younger age at onset, which is frequently associated with more extensive lesions of neural substrates, as seen above. Lesion related impairments might become increasingly evident when the brain matures.

As for other predictors, the extent of the impact of the predictor duration of epilepsy on EF remained relatively small despite significance. Further, patients with ongoing seizures after epilepsy surgery were not excluded from the analysis of duration of epilepsy, potentially overcasting an increase of performance of EF for the seizure free group. However, 6 months after surgery there were only three patients and one patient 5 years after surgery, which had no worthwhile improvement of seizures after surgery. All other patients were seizure free or had significant improvements of their seizures. Most importantly, an effect of seizure outcome after surgery on EF was not found, which will be presented and discussed below.

4.2.8. Seizure Outcome

Surprisingly, in this study at hand, post-surgical seizure outcome did not influence EF development, neither in the short nor long-term. For almost all EF, abilities were stable and in the lower average, over time. Two subgroups were compared, the completely seizure free group (Engel outcome class 1a) versus the non seizure free group (all other Engel outcome class from 1b to 4).

It is possible that the severe criterion, the intent to compare really seizure free patients (Engel class 1a) to patients who still had seizures, even though most had very occasional seizures (e.g., group Engel classes 1b and 1c), did mask a potentially beneficial effect of seizure reduction due to surgery. In most studies, the seizure free group is composed of the complete Engel 1 outcome group, so patients from Engel outcome groups 1b-d are included, who still have very occasional epileptic seizures after surgery (e.g., Freitag & Tuxhorn, 2005; Ramantani et al., 2018). However, even with this less severe criterion, results in other studies are inconclusive regarding the effect of seizure outcome on cognitive functions: Many authors have found no effect of seizure freedom on cognition (D´Argenzio et al., 2011; Lendt et al., 2002; Smith et al., 2004; Puka & Smith, 2016), whereas others found improvements in seizure free groups in IQ (Freitag & Tuxhorn, 2005; Puka et al., 2017), in processing speed (Hallböök et al., 2018) and in memory (Martin et al., 2016; Kaur et al., 2022). Studies on the effect of seizure outcome on EF could not be found.

In the study at hand, seizure presence after surgery does not seem to impact EF development significantly. However, the duration of epilepsy prior to surgery did influence EF: The longer the duration of epilepsy was before the surgical intervention, the more EF were negatively impacted, the less EF were developing. This observation could be explained by the pathological neural substrate underlying the epileptic seizures, which is negatively influencing brain networks including those responsible of EF development, and its removal during surgery stops its deteriorating effect. The seizures themselves would not negatively impact EF but would rather be seen as a symptom of the underlying, malfunctioning brain tissue. It might also be possible that the postsurgical evaluation time of maximum 5 years is not long enough to show significant effects of seizure freedom on EF. Puka, Tavares and Smith (2017) for instance, found positive effects of seizure freedom on intelligence in a paediatric surgical group after 4-11 years after surgery. Another important aspect, which will be discussed further in the next topic, is ASM load. In our cohort, only 25% of patients were ASM free 60 months after surgery, despite 65% of completely seizure freedom since surgery (Engel outcome class 1a). This very conservative and cautious procedure of ASM reduction in our German cohort is not what is commonly done in postsurgical cohorts. For instance, in an international, multicenter cohort, 54% had completely discontinued ASM 5 years after surgery (Boshuisen et al., 2012). ASM load is known to impact significantly cognitive performances (Besag & Vasey, 2021). So, it is possible that the seizure free group in our cohort was still under the influence of a higher ASM load, which might have reduced the potential benefit of seizure freedom on cognition, reported in other studies.

4.2.9. ASM Load

ASM load is a very important potential predictor of cognitive outcome since it is one of the only modifiable variables in epilepsy surgery. As reported above, the amount of ASM, especially the number of different ASM taken by a patient can greatly influence his or her cognitive performance (Besag & Vasey, 2021). The negative effect of ASM on cognition, and particularly on EF in non- and presurgical groups is well documented (Helmstaedter et al., 2010; Kadish et al., 2013; Hamed et al., 2009). Regarding surgical cohorts, Vogt and colleagues (2018) found a negative correlation between EF and higher ASM load after temporal tumor surgery. ASM reduction has been associated with IQ improvement after epilepsy surgery (Boshuisen et al., 2015; Skirrow et al., 2011). Especially processing speed is reported to improve significantly after ASM reduction (Van Schoonefeld et al., 2013; Hallböök et al., 2013).

In our study, the ASM load influenced Planning abilities as well as Working Memory, but did not have an effect on Problem Solving, Fluency, Inhibition or Flexibility. The factor time did not influence any EF in their development, nor did any interaction effects between ASM load and time exist. ASM reduction significantly improved Planning abilities after surgery: Post-hoc analyses revealed differences in favour of the ASM free group 2 and 5 years after surgery. For Working Memory, patients without ASM did better than patients with one or more ASM before surgery and also 12 months after surgery. In our study the task Symbol Search, used to explore Flexibility, is also a task which is employed to evaluate processing speed. Improved speed in groups with less or no ASM, as found in other studies (Van Schoonefeld et al., 2013; Hallböök et al., 2013), could not be replicated in this present study.

One possible explanation for the absence of improvement for 4 out of 6 evaluated EF tasks and the changes in Planning and Working Memory which remain small in amplitude, might be due to surgery itself: The very cautious approach to reduction in ASM in our cohort means that only patients with complete lesion removal and with a very low risk for seizure reoccurrence, had a total ASM withdrawal. These patients usually have larger resection sites to secure seizure freedom, at the same time they encounter more risks for cognitive decline if functional tissue is removed. On the other hand, patients who are still taking ASM years after surgery are still under the influence of the negative side effects of ASM on cognition. Overall, this might explain the – smaller than expected- differences between the ASM free group and the 2 ASM groups. Another possibility is that the sample sizes are too small to show significant

differences, or the observation time of 5 years is not long enough. Other authors have postulated before that improvements due to medication reduction might take years to manifest (Kaur et al., 2022; Skirrow et al., 2019). For instance, in the Fluency task, when analysing the means– the "more than one ASM" group (>1 – group) stagnated between 24 and 60 months after surgery whereas the two other groups (ASM free and one ASM) showed increased means representing improvement, despite significance. Hypothetically, it is also possible that the negative long-term effect of ASM on a developing brain, especially on EF during sensitive developmental phases, persists even after drug withdrawal as it can happen during exposure to ASM during pregnancy. This has not yet been thoroughly investigated due to methodological difficulties because of the observational nature of most studies on children using ASM, but has been suggested (Kellog & Meador, 2017). However, the impairment in EF in our cohort remains small, since the mean performances of the 3 ASM groups are in the lower norm for most tasks at most evaluation times. It might be of importance to analyse which ASM were prescribed before surgery and which one has been discontinued at first after surgery, as one might think that ASM with known cognitive side effects (e.g. valproic acid, phenobarbital, phenytoin, topiramate) would be discontinued earlier after surgery.

4.3. Analyses of Potential Predictors in Subgroups With Significant EF Change After Paediatric Epilepsy Surgery

After group-level analyses, the distribution of changes of at least one standard deviation in magnitude in EF test scores, from the presurgical evaluation to the postsurgical neuropsychological evaluation 2 years after surgery was examined. This simple method for measuring change in individuals has also been used in other studies (i.e. Martin et al., 2016; Van Schoonefeld & Braun, 2013; Smith et al., 2004). On a clinical basis, one can expect a change of one standard deviation in neuropsychological tests to bring significant change in daily life of patients.

Despite the association of higher scores across most EF and the clinical variables older age at epilepsy onset, a shorter duration of epileptic seizures until surgery, a higher presurgical IQ and a left hemispheric surgery, only a few patients showed significant improvements or deteriorations. The distribution of improvements and deteriorations for the different clinical factors and the different EF tasks is presented in Figures 4 and 5, in chapter 3.4.

Except for a descriptively higher presurgical IQ in the group which improved at the Planning task and for which a trend towards significance could be established, all other analyses were not significant. However, effect sizes were often in the small to medium range, so it could

be possible, that comparisons between improved and declined patients might have become significant if sample sizes were larger. For instance, in accordance with group analyses, all EF tasks showed small to medium effect sizes for side of surgery with more declines in the right-resected group. For the EF Planning, medium effects were found for presurgical IQ, for side of surgery and for seizure outcome in favour of the seizure free patient group. Medium effects were also found for Working Memory with lower presurgical mean IQ in the improved group.

Interpretations of these results are not reasonable due to the very small sample sizes: For a cohort of 117 patients, the EF task with the most improvements over one standard deviation was Planning, and only as few as 17 patients (15%) improved to this extent. Declines over one standard deviation were even rarer: The largest decline group was found for the Problem Solving task, with only 11 patients (9%) showing decreased performance. Other declines and increases were around 1-8% per task. The traditional one-SD-methodology is often criticized for overestimating postoperative improvements and declines in comparison to the Reliable Change Index method (RCI). Surprisingly, Kaur and colleagues (2022) analysed individual change with the RCI method and found higher percentages of significant decline and improvement for most evaluated tasks after paediatric epilepsy surgery (9-34% of significant changes per task). They also found more declines than improvements in different EF. For instance, for Working Memory, they found 13.8% decline and 13.2% increase, in this study at hand 9% increase and 3% decline were found. For Fluency, Kaur and colleagues (2022) found 22.2% declines and 13.9% increases, whereas in this study 8% and 9% were found, respectively. However, Kaur and colleagues evaluated individual change between the presurgical evaluation and the first postsurgical evaluation, 6.5 months after surgery, whereas in the current study the presurgical and evaluation 24 months after surgery, were compared, which might explain the difference.

Some studies which focused on outcome on an individual level have found that despite a better global cognitive surgical outcome for higher presurgical IQ, postsurgical significant increases are more frequent in patients with severe impairment, mostly due to the interruption of epileptic encephalopathy and a “restart” or acceleration of cognitive development (Ramantani & Reuner, 2018; Ramantani et al, 2018b; Kaur et al., 2022). This effect cannot be observed in this study since children with severe cognitive impairment were excluded from the study.

On an individual, clinical basis, our results are encouraging: Large improvements in the analysed EF are not to be expected after epilepsy surgery, however, a rather stable EF outcome

can be hoped for, with only very rare significant post-surgical declines in our large surgical cohort.

4.4. Strengths and Limitations

The current study was the first, to our knowledge, to investigate multiple executive functions in the long-term, in a cohort of paediatric epilepsy surgery patients. Research up to date has mainly focused on intellectual outcome, because a lot of data could be gathered since most of the studies are retrospective and IQ test batteries usually represent the heart of the neuropsychological evaluation in children, as a cumulative measure of different cognitive abilities (Baxendale et al., 2016; Flanagan et al., 2013). This study at hand focuses on EF, which have been shown to be of upmost importance for academic achievement (Zelazo & Carlson, 2020; Raghubar et al., 210; Butterfuss & Kendeou, 2018), for self-regulatory behavior (Doebel, 2020) and for adapting to different kind of novel situations, both in academic and in daily life contexts (Diamond, 2020). The study results showed, that paediatric epilepsy surgery is a safe treatment option for intractable epilepsy regarding EF: EF either improve over time or do not change significantly, neither right after surgery nor in the long run. Individual declines and improvements are possible after surgery, but rather the exception (0-15%). The use of a heterogeneous cohort in terms of surgical localization allowed for a representative sample of epilepsy surgery patients, so our findings can be generalized to this population. Subsequent explorative analyses of different clinical variables, such as surgical localization, etiology of lesion and side of surgery showed which variables impacted the EF outcome and which were negligible. The value of this study was the long-term follow- up on multiple variables, evaluating the complexity of these children with intractable epilepsy undergoing surgery. A limitation of this current study is the missing comparison group as an adequate control condition. This is an ethical dilemma of epilepsy surgery outcome research in general. Control groups comprising children with drug-resistant epilepsy who were rejected from epilepsy surgery programs, have sometimes been used in research (Danielsson et al., 2009; Puka & Smith, 2016). These children were usually considered not suited for surgery for various epilepsy related reasons such as anterior multilobar extension of lesion, bilateral lesion, or epileptogenic zone in an eloquent area or an underlying genetic disorder. It remains questionable if these patients represent an appropriate, comparable control group for neuropsychological outcomes, since most of these epilepsy features have been recognized as significantly impacting cognitive functioning. Controlled randomization, as used in medical treatment efficacy studies, is not permitted in epilepsy surgery (Hoppe et al., 2023). Hoppe and colleagues (2023) proposed to

partially compensate for the limitation of missing an appropriate control group by using within-sample comparisons, which were done in this research. Further, each child was also compared with him- or herself over the course of 5 neuropsychological evaluations, as well as to the normative, age-matched population. However, the absence of an adequate control group needs to be considered when interpreting the present results regarding the impact of surgery on EF. The possibility of significant changes being due to other factors remains.

As in many other studies in the epilepsy surgery research field, the current study is retrospective, which brings its challenges: Because not all tests from the perisurgical neuropsychogical protocol were administered or because patients did not show up at all 5 evaluation times, missing data was frequent. Therefore, traditional statistic methods such as repeated measures ANOVA could not be performed and needed to be replaced by the more complex Multilevel models. Also, a factor analysis, such as the principal component analysis (PCA), which was initially planned to be performed to evaluate the validity of the EF test battery in epilepsy patients used in the current study, was not feasible due to missing data. A prospective study would contain and reduce the risk of missing data, however it would take years to collect sufficient patient data to enable research.

EF did either not change over the course of time and after surgery or they improved, to a small extent. Gains of a few points in some EF could either be improvement of ability or reflect sustainability of EF over the course of time (Schmidlechner et al., 2023). In the second case, significant gains could be explained by two phenomena: First, practice effects could explain the small gains. Except for Fluency, no parallel version of the test exists, so the same material was administered up to 5 times to the patients. The unanticipated novelty of tasks, which requires significant EF involvement, was therefore not given. However, considerable time was lying between the 4th and 5th evaluation, probably erasing the effect of repetition. Also, negative practice effects have also been reported in epilepsy patients regarding EF, typically in Working Memory and in processing speed tasks (Hermann et al., 1996; Busch et al., 2015). Second, the statistical tendency of high and low scores to progress towards the mean during subsequent neuropsychological evaluations cannot be ruled out (“regression towards the mean”, Bland & Altmann, 1994). Multilevel models do not account for this phenomenon but regression coefficients for continuous variables in the current study did not point into this direction.

Further, a selection bias, especially in the 5 years postsurgical evaluation group, is possible: Only one fourth of the surgical cohort presented itself to this postsurgical evaluation. Seizure outcome in this group is comparable to the evaluations the years before. However, the probability is high that patients which became seizure free, have a good quality of life and are

not bothered by neuropsychological deficits, did not follow the invitation for the 5 years post-surgical follow-up, which included a 3-day hospital stay. Therefore, the long-term outcome of the current study might be underestimating improvements.

4.5. Implications

Only a moderate number of aspects of EF was examined in this study, so new investigations should be aimed at other EF skills. Further, test impurity is a well-known difficulty in neuropsychological assessment, as no task can be a pure measure of one executive or cognitive function. For instance, Inhibition is always Inhibition of something (a distractor variable, a thought etc.), so other cognitive functions are always involved (Friedman & Miyake, 2004; Diamond, 2020). Prospective studies on EF development in the context of paediatric epilepsy surgery are much needed, including tests, which have been proven to validly evaluate EF (i.e. Epitrack Junior, WCST, ToL, TMT; Helmstaedter et al., 2019; Kadish et al., 2013).

More prospective research on the long-term outcomes of EF after paediatric epilepsy surgery is also necessary, to confirm our encouraging results. A prospective design might lead to less early drop-outs and reduce the possible bias of a "worse than reality" patient cohort at the 5 years post- surgical evaluation. Further, in the study at hand, the focus was on cognitive, or "cold" EF, which have an important impact on academic skills (Zelazo & Carlson, 2020). We are unaware of any study that has investigated "hot" EF, the social and emotional aspects of EF including emotional regulation, theory of mind and behavioral Inhibition control in paediatric epilepsy surgery cohorts. For health care professionals, patients and families to develop realistic expectations in the context of paediatric epilepsy surgery, research combining the observation of long-term development of cold and hot EF would be very helpful.

Our current study leads to another question: is it necessary to evaluate EF at every postsurgical evaluation? The changes are modest, often not significant between two consecutive postsurgical evaluations. A first postsurgical evaluation to determine immediate losses due to surgery and necessity for rehabilitation services to intervene would be sufficient, followed by a second postsurgical evaluation years later (2 to 5) to check if significant changes, which impact daily living and school or work performances, occurred and if the rehabilitative care and academic adaptations need to be reevaluated. Given similar results in post-surgical IQ-research, the postsurgical neuropsychological evaluations could be shortened, ultimately reducing health care costs.

4.6. Conclusion

The main findings in this present research indicate that epilepsy surgery can be considered a safe treatment option for refractory epilepsy in children and youth regarding the outcome of executive functions. The analyses of longitudinal developmental pathways of seven different EF before and up to 5 years after paediatric epilepsy surgery gave reassuring results.

In a representative cohort of 117 paediatric epilepsy patients, who underwent epilepsy surgery in two German epilepsy centres, 65% were completely seizure free (Engel outcome class 1a) 5 years after surgery. The investigation of longitudinal EF outcome revealed that none of the EF presented a lasting deficit after the surgical intervention. Just as for IQ in surgical paediatric epilepsy cohorts, EF were mostly in the lower average before surgery (Boshuisen et al., 2015). After surgery, patients either maintained their level or they improved to be at the average performance level. These significant improvements on a group level corresponded to rather small changes in mean scores, usually less than one standard deviation of change over the course of 5 years, so these gains seemed to indicate sustainability or lightly increased EF development after surgery.

Planning improved over time, an Inhibition task also showed improvement, another Inhibition task as well as Problem Solving and Monitoring did not change over time, Flexibility and Working Memory decreased right after surgery and improved over the course of the following years, Fluency improved right after surgery. Different plastic brain processes might explain these results: An increase of performance after surgery can be due to the functional release of neighbouring brain areas after cessation of epileptic activity (as in Moosa & Wyllie, 2017), which will result in a restart of development. Unanswered remains the question whether the involved plastic process is a perilesional reorganization after the removal of dysfunctional tissue (Lidzba et al., 2019) or if the contralateral hemisphere takes over the function of the surgical hemisphere. Contralateral takeover was first proposed for hippocampal postsurgical functions after temporal lobe epilepsy surgery by Chelune in 1995, who called it the `functional reserve model´. This model has since been expanded to other functions localized in other brain areas (i.e. in Kaur et al., 2022). It is supposed to be more frequent in abilities which are typically lateralized like verbal or visual information processing.

Decreases after surgery could be explained by the `functional adequacy theory´, the second proposition of Chelune´s theory of outcome after temporal lobe surgery (1995), which has been expanded beyond the scope of temporal lobe surgery by Moosa and Wyllie (2017), as well as by Kaur and colleagues (2022). This model hypothesizes that there is loss of retained

function in the surgical area due to removal of functional brain tissue (Moosa & Wyllie, 2017). In this research at hand, decreases were usually followed by slow improvements over time, which again speaks for brain plasticity in the sense of improvement due to activation or overtake by either perilesional brain tissue or the nonsurgical hemisphere. This effect of improvement over time has been described in other studies on epilepsy surgery in children and adolescents for other cognitive functions such as intellectual functioning, memory, and language (Helmstaedter & Elger, 1998; Skirrow et al., 2011; Gleissner et al., 2005; Puka et al., 2017).

In conclusion, development of EF after surgery in young patients appears to depend on different consecutive and intertwined plastic processes. Functional imaging studies have shown that the underlying neural substrate of EF shares a functional basis, a common brain network, but at the same time, each EF seems to be taking a particular pathway within this network (Niendam et al, 2012; Udin et al., 2019). This is supported by studies in cognitive neuropsychology, which have led to the creation of the unity and diversity model of EF (Friedman & Miyake, 2017). The study at hand supports these findings, as the different EF take different developmental pathways.

Explorative analyses of clinical factors paired with time passing since the presurgical neuropsychological evaluation, allowed to find predictors of EF outcome in this study. Explorative post-hoc analyses were performed despite not always significant main effects, as recommended for explorative studies. Its purpose is to reveal significant effects between subgroups, which would stay masked otherwise, and which could emphasize the need for further studies. The potential predictors of EF outcome were presurgical IQ, side of surgery, etiology, surgery type, localization of surgery, age at onset of epilepsy, duration of epilepsy prior to surgery, postsurgical seizure outcome and ASM load.

A higher presurgical IQ predicted a higher postsurgical EF performance for all EF, and mostly without an evolution over time. These results are not surprising, considering the strong correlation between IQ and EF (Diamond et al., 2013).

Further, left sided surgery was a significant predictor of better postsurgical EF outcome in four out of six investigated EF. One explanation could be atypical language lateralization in a large part of the cohort, as described by Helmstaedter and colleagues (2006). A more plausible explanation could be complex reorganizational and compensatory processes, as shown before in paediatric cohorts (Nagel et al., 2013). Postsurgical declines, especially for the verbal EF Working Memory and Fluency, were not shown on a group level, which might be due to rigorous presurgical selection and exclusion of patients with lesions in eloquent areas. Increases in left-sided surgical patients probably became possible due to presurgical reorganizational

processes because of the preexisting lesion as well as functional release mechanisms after the excision of the epileptogenic zone. The visual modality-based EF tasks Flexibility and Problem Solving also improved more in the left-sided surgery group. Visuospatial abilities are typically supported by the right hemisphere. Therefore, contralateral functional release mechanisms after cessation of the generalized seizure activity due to surgery, as described in the adapted function adequacy model (Kaur et al., 2022) might explain the results.

Etiology was a significant predictor of outcome for the EF Problem Solving, Fluency and Working Memory. Despite considerable missing data, a tendency for subgroups with more localized lesions such as tumor patients and mesiatemporal sclerosis patients to have better EF outcomes, was evident.

Surgery type did not have a significant impact on most EF, as in previous research (Sherman et al., 2012). Explorative post-hoc analyses showed varying patterns of effects for the surgical groups for the different EF. The intralobar tailored resections group, which consisted mostly of resections within the frontal lobe, had lower performances than the rest of the cohort before and right after surgery in Planning and Working Memory, possibly reflecting disturbances before surgery within the fronto-parietal cognitive control network (Niendam et al., 2012). This hypothesis was further supported by a similar pattern for the frontal surgery group, in the analysis of the factor localization. After surgery a slow and steady increase in performance was observed for both groups. Further, the lesionectomy group, the temporal tailored + AHE group and the standard temporal resection ± AHE group improved in Fluency. Multilobar surgeries, despite large resection sites, did only show lower performances than the mean and no improvement over time for Inhibition, for other EF they were at mean cohort level. The EF Inhibition might be particularly sensitive to extended lesions, whereas most EF are not majorly impacted by large, posterior lesions.

The analyses of the effect of localization and time on different EF also showed varying patterns of significance for the different subgroups, as for the analysis of surgery type. However, the frontal and the parietal surgical subgroups stood out. The frontal subgroup had lower performances after surgery than the mean in Planning, Fluency and Working Memory. Performance increased slowly afterwards, reaching the mean level after two to five years. The same pattern of development was observed for the parietal subgroup for Problem Solving, replicating previous results (Gleissner et al., 2008). This speaks for the presence of functional tissue in the surgical area, leading to postsurgical decline. Then plasticity operated to lead to a restart of development and reach the mean level of the cohort 24 to 60 months after surgery. It is not surprising that these two localizations groups were impacted, since neuroimaging has

shown that EF functions activate a fronto-cingulo-parietal network, the cognitive control network (Niendam et al., 2012).

Age at epilepsy onset was a significant predictor of EF outcome: The higher the age at epilepsy onset, the higher were the scores on EF tasks. This was true for all investigated EF. However, time passing from presurgical to 5 years postsurgical intervention, did not have a significant effect on EF outcome for Problem Solving, Fluency, Working Memory and Inhibition. For Planning and Flexibility, the effect of age at onset even increased over time. The protective effect of older age at seizure onset for EF implies that a younger age at onset hinders an adequate EF development. It also means that the effect of age at seizure onset persists beyond surgery and over the course of 5 years and that surgery does not allow to inverse that tendency, neither does time passing after surgery. Studies on other cognitive functions like memory have already described the negative effect of a young age at seizure onset (Ramantani & Reuner, 2018).

Duration of epilepsy was a significant predictor of EF performance, already prior to surgery. The longer the seizure duration was, the more negatively impacted were EF. There was no significant change, neither right after surgery, nor with time passing. This result emphasizes the need for an early intervention, which has already been expressed in other studies on IQ and memory (Ramantani et al., 2014; Gleissner et al., 2005).

Seizure outcome did not predict EF in this study at hand. Patients in the Engel outcome class 1a compared to patients in all other Engel outcome classes, did not differ significantly in the different EF. Other authors, investigating other cognitive functions in the paediatric epilepsy surgery context such as memory and processing speed also did not find an effect of seizure freedom (Lendt et al., 2002; Puka & Smith, 2016). Maybe the 5 years postsurgical observation of EF outcome was not long enough to see changes, or the ongoing ASM intake, which was considerable in the cohort at hand (75% at 5 years post-op) masked potentially positive effects of seizure freedom on EF.

ASM load is known to impact EF (Helmstaedter et al., 2010; Kadish et al., 2013). A higher ASM load is negatively influencing EF, whereas the stop of ASM intake is associated with IQ improvement as well as higher processing speed (Boshuisen et al., 2015; Van Schoonefeld et al., 2013). In this study at hand, a lower ASM load was linked to better Planning and Working Memory abilities, independent of time passing. The changes were small in amplitude, though. ASM load did not have an impact on processing speed. ASM load did also not influence Problem Solving, Fluency, Inhibition, or Flexibility. This missing positive effect of medication reduction might be explained by the conservative ASM reduction in this cohort.

65% of patients were completely seizure free 5 years after surgery, but only 24% had discontinued ASM, compared to 54% of total ASM withdrawal in an international cohort (Boshuisen et al., 2012). So only patients with complete lesion removal, and therefore higher risk of cognitive decline due to larger resection, must have withdrawn all ASM, and many seizure free patients were still under the negative influence of ASM on cognition, which might explain why the differences between both groups were smaller than expected. There might also be a lasting negative effect of ASM on EF in the immature brain, despite withdrawal, as it has been described for prenatal ASM exposure (Kellog & Medor, 2017).

After analyses on cohort-level, the subgroups of patients with changes of at least one standard deviation in magnitude in EF test scores were evaluated, using the data of the 3rd postsurgical neuropsychological assessment, two years after surgery. All analyses were non-significant, none of the possible predictors explained significant change on an individual level. Despite inconclusive comparisons, effect sizes were often in the small to medium range, for instance a medium effect size for side of surgery with worse outcome in right-resected patients and also a medium effect size for Working Memory with lower IQs for improved patients. The sample sizes were very small, below 18 patients, as only a few patients out of 117 showed significant EF increase or decrease 24 months after surgery, which might explain why none of the comparisons were significant. In conclusion, as for the outcome of EF after paediatric epilepsy surgery on a cohort level, the analyses of patient subgroups with significant EF change is also reassuring, because significant EF change and especially large declines are rare.

The value of this study at hand is the investigation of a set of EF in the long-term in a representative sample, a large paediatric epilepsy surgery cohort. To our knowledge, it is the first study to focus on EF to this extent. Further long-term outcome research, if possible prospective and including a control group, will be needed to confirm our results. This study is retrospective and encounters typical challenges such as missing data, especially in test scores as well as in sample sizes, i.e. for certain localization and surgery type subgroups, as well as small sample sizes in the 5 years post-surgical group. Especially prospective studies with planned long-term evaluations after epilepsy surgery, will enable to have sufficiently large, unbiased groups for evaluating the EF outcome. Certain clinical factors have been shown to be predictors of postsurgical outcome of other cognitive functions such as intellectual functioning, memory, and language in previous research. This study allowed to extend the influence of some of these factors to the post-surgical, long-term outcome of EF. These predictors were presurgical IQ, age at epilepsy onset and duration of epilepsy prior to surgery. New interesting results on the effects on EF of frontal and parietal localizations, on localized etiologies like

tumors were revealed. Surgery type did not appear to be an important predictor of EF outcome, neither did seizure outcome nor ASM load, which was unexpected.

In this paediatric cohort, reorganizational and compensatory processes were probable up to 24 and 60 months after surgery, since small improvements were ongoing. As reported above, paediatric epilepsy surgery can be considered a safe treatment option regarding EF development. Further prospective, long-term research is needed and could include ecological measures to evaluate the impact of EF on the young patients ‘daily life on their transition to adulthood.

5. Summary

The aim of this study was to investigate the longitudinal development of executive functions (EF) after epilepsy surgery in children and adolescents. EF are cognitive functions, which are crucial for academic achievement, self-regulatory behaviour, and adaptation to novel situations. The research questions were the following: How did the different EF Working Memory, Inhibition, Monitoring, Flexibility, Planning, Problem Solving and Fluency, develop in a paediatric epilepsy cohort after surgery, over the course of five years? How did clinical factors, such as etiology and localization of surgery, affect the development of EF in this context? Which of these potential predictors distinguished patients, who had significant increases of EF after surgery from those who had significant declines? Longitudinal data of a clinical cohort of 117 children and adolescents who underwent epilepsy surgery in two German epilepsy centres between 1996 and 2016 was analysed exploratively and retrospectively. Mean age at surgery was 12;10 years (*standard deviation* = 3;10). Before surgery, as well as 6, 12, 24 and 60 months after surgery, patients underwent a neuropsychological assessment, including tasks evaluating the different EF listed above. The statistical analyses included descriptive statistics as well as explorative analyses of development of the 7 investigated EF over the course of 5 assessment times. Univariate and multivariate Multilevel Models were considered most appropriate for the data analysis. In each univariate model, the time between examinations was the independent variable and one of the different EFs was the dependent variable. In the multivariate models, time and a clinical factor were included in the model as independent variables and one of the EFs as the dependent variable. Explorative post-hoc analyses using estimated marginal means, pairwise comparisons and/or deviation contrasts were calculated. For continuous variables, regression coefficients were reported. These analyses of the whole cohort were followed by analyses of subgroups of patients with significant change. Patients with a change of at least one standard deviation on an EF task between the presurgical and the 24 months post-surgical evaluation were selected for these analyses. Potential differences in clinical variables between patients with decreased or with improved EF performances were explored using χ^2 or Fisher's exact test for categorical independent variables, and the unpaired t-test, the Welch t-test or the Mann-Whitney-U-Test for the continuous independent variables, as appropriate. On a group level, the means of all EF were in the lower average before surgery. Univariate analyses showed that Fluency improved at the first postsurgical evaluation, Working Memory and Planning improved in the years after surgery, Inhibition, Problem Solving, Monitoring and Flexibility did not present a significant change. Improvements were small in amplitude, usually below one standard deviation. The main results of multivariate analyses and

explorative post-hoc analyses were the following: A higher presurgical intelligence quotient, left-hemispheric surgery, the etiologies tumor and mesiotemporal sclerosis, localization outside of frontal and parietal lobes, an older age at epilepsy onset and shorter duration of epilepsy all predicted a better postsurgical long-term outcome of EF. Surgery type, seizure outcome and antiseizure medication load did not have significant effects on long-term EF outcomes. Some subgroups presented post-surgical declines, but a slow and steady increase over time mostly allowed to reach the group mean within 5 years. For the subgroups with significant change, none of the clinical variables allowed to differentiate between patients who showed significant improvement versus patients who presented a significant decline between the presurgical and the 24 months-post-surgical evaluation. Only 3%-15% of the cohort experienced changes of at least one standard deviation in EF after surgery. Declines after surgery could be explained by resection of brain tissue, which still carried function prior to surgery. Increases over time could be explained by plasticity and compensatory processes, such as contralateral takeover or perilesional reorganization. Improvement appearing right after surgery might be explained by release of reserve capacities in regions, which were dysfunctional due to epileptic irritation prior to surgery.

In conclusion, paediatric epilepsy surgery can be considered a safe treatment option regarding EF. Prospective studies on long-term outcome of various EF are needed to confirm these results. The study at hand constitutes the first long-term study focused on EF development in a large, representative paediatric epilepsy surgery cohort.

Zusammenfassung

Ziel dieser Studie war die Untersuchung der Längsschnittentwicklung exekutiver Funktionen (EF) nach Epilepsieoperation bei Kindern und Jugendlichen. EF sind kognitive Funktionen, die für schulische Leistungen, selbstregulierendes Verhalten und die Anpassung an neue Situationen entscheidend sind. Die Forschungsfragen lauteten wie folgt: Wie entwickeln sich die verschiedenen EF (Arbeitsgedächtnis, Inhibition, Monitoring, Flexibilität, Planung, Problemlösung, Wortflüssigkeit) in einer pädiatrischen Epilepsiekohorte nach der Operation im Laufe von fünf Jahren? Wie beeinflussten klinische Faktoren wie u.a. die Ätiologie und die Lokalisation der Operation, die Entwicklung der EF? Welche dieser potenziellen Prädiktoren unterschieden Patienten, deren EF sich nach Operation signifikant verbesserten, von denen, deren EF sich signifikant verschlechterten? Retrospektiv und explorativ analysiert wurden Längsschnittdaten einer klinischen Kohorte von 117 Kindern und Jugendlichen, die zwischen 1996 und 2016 in zwei deutschen Epilepsiezentren epilepsiechirurgisch behandelt wurden. Das mittlere Alter bei der Operation betrug 12;10 Jahre *(Standardabweichung* = 3;10). Vor der Operation sowie 6, 12, 24 und 60 Monate nach der Operation nahmen die Patienten an einer neuropsychologischen Untersuchung teil, die auch Aufgaben zur Beurteilung der verschiedenen oben genannten EF umfasste. Die statistischen Analysen umfassten sowohl deskriptive Statistiken als auch explorative Analysen der Entwicklung der 7 untersuchten EF im Verlauf von 5 Untersuchungszeitpunkten mittels univariaten und multivariaten Mehrebenenmodellen. Bei jedem univariaten Modell war die Zeit zwischen den Untersuchungen die unabhängige Variable und eine der verschiedenen EF die abhängige Variable. Bei den multivariaten Modellen wurden Zeit und ein klinischer Faktor als unabhängige Variablen sowie je eine der EF als abhängige Variable in das Modell inkludiert. Es wurden explorative Post-hoc-Analysen mit geschätzten marginalen Mittelwerten, paarweisen Vergleichen und/oder Abweichungskontrasten berechnet. Für kontinuierliche Variablen wurden Regressionskoeffizienten angegeben. An diese Gruppenanalysen schlossen sich Analysen von Untergruppen an. Für diese Analysen wurden Patienten mit einer Veränderung von mindestens einer Standardabweichung bei einer EF-Aufgabe zwischen der präoperativen und der 24-monatigen postoperativen Untersuchung ausgewählt. Potenzielle Unterschiede in den klinischen Variablen wurden je nach Bedarf, zwischen Patienten mit verminderten oder verbesserten EF-Leistungen mit dem χ^2-Test oder dem exakten Test von Fisher für kategoriale unabhängige Variablen und mit dem ungepaarten t-Test, dem Welch t-Test oder dem Mann-Whitney-U-Test für die kontinuierlichen unabhängigen Variablen

untersucht. Folgende Ergebnisse wurden gefunden: Auf Gruppenebene lagen die Mittelwerte aller EF vor der Operation im unteren Durchschnitt. Univariate Analysen ergaben, dass sich die Wortflüssigkeit zur ersten postoperativen Untersuchung verbesserte. Das Arbeitsgedächtnis und die Planung verbesserten sich in den Jahren nach der Operation, während Inhibition, Problemlösung, Monitoring und Flexibilität keine signifikanten Veränderungen aufwiesen. Die Verbesserungen waren gering und lagen in der Regel unter einer Standardabweichung. Die wichtigsten Ergebnisse der multivariaten Analysen und der explorativen Post-hoc-Analysen waren die folgenden: Ein höherer prächirurgischer Intelligenzquotient, eine linkshemisphärische Operation, die Ätiologien Tumor und mesiotemporale Sklerose, eine Lokalisation außerhalb des Frontal- und Parietallappens, ein höheres Alter bei Beginn der Epilepsie und eine kürzere Dauer der Epilepsie sagten alle ein besseres postoperatives Langzeitergebnis der EF voraus. Die Art der Operation, die Anfallssituation nach der Operation und die Anzahl der Antianfallsmedikamente hatten keine signifikanten Auswirkungen auf die langfristigen EF-Ergebnisse. In einigen Untergruppen kam es nach der Operation zu einer Verschlechterung der EF, aber ein langsamer und stetiger Anstieg im Laufe der Zeit ermöglichte es den meisten, den Gruppendurchschnitt innerhalb von 5 Jahren zu erreichen. Auf individueller Ebene erlaubte keine der klinischen Variablen eine Unterscheidung zwischen Patienten, die eine signifikante Verbesserung aufwiesen, und Patienten, die zwischen der präoperativen und der 24-monatigen postoperativen Auswertung eine signifikante Verschlechterung zeigten. Lediglich bei 3-15 % der Kohorte kam es nach der Operation zu Veränderungen der EF um mindestens eine Standardabweichung. Verschlechterung nach der Operation könnte durch die Resektion von Hirngewebe erklärt werden, das vor der Operation noch funktionstüchtig war. Verbesserungen im Laufe der Zeit könnten durch Plastizität und kompensatorische Prozesse, wie kontralaterale Übernahme oder periläsionelle Reorganisation, erklärt werden. Die unmittelbar nach der Operation auftretende Verbesserung könnte durch die Freisetzung von Reservekapazitäten in Regionen erklärt werden, die vor der Operation aufgrund der epileptischen Reizung dysfunktional waren. Zusammenfassend lässt sich sagen, dass die pädiatrische Epilepsiechirurgie als eine sichere Behandlungsoption hinsichtlich EF angesehen werden kann. Um diese Ergebnisse zu bestätigen, sind prospektive Studien zu den Langzeitergebnissen der verschiedenen EF in diesem Kontext erforderlich. Bei der vorliegenden Studie handelt es sich um die erste Langzeitstudie, die sich auf die Entwicklung der EF in einer großen, repräsentativen pädiatrischen epilepsiechirurgischen Kohorte konzentriert.

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7. Eigenanteil an Datenerhebung und -auswertung und eigene Veröffentlichungen

Diese Arbeit wurde im Rahmen der Kooperation zwischen der Sektion für Neuropädiatrie und Stoffwechselmedizin des Universitätsklinikums Heidelberg sowie des Epilepsiezentrums der Diakonie Kork unter dem Projektnamen EXE-EPI durchgeführt. Die testpsychologischen Befunde wurden von sämtlichen psychologischen und neuropsychologischen MitarbeiterInnen, die im Zeitraum von 1998-2017 an den beiden oben genannten Zentren Untersuchungen durchgeführt haben, erhoben: In Heidelberg waren in hohem Maße Frau Prof. Dr. Gitta Reuner sowie Frau Dr. Navah Kadish beteiligt, einige PatientInnen wurden von Frau Doreen Balke und Frau Christine Schütz untersucht. In Kehl-Kork wurden die PatientInnen vor allem von Herrn Dr. Hans Mayer, Frau Dr. Sylvia Schneider, Herrn Werner Christ, Frau Bettina Gomer und mir untersucht. Die Patientendaten wurden retrospektiv von mir erhoben, die Auswertung der Daten erfolgte ebenso durch mich und stellt das zentrale Ergebnis dieser Dissertation dar.

Teilergebnisse der vorliegenden Arbeit wurden in Form eines Poster-Abstracts vorab publiziert:

Kämpf, M., Bast, T., Mayer, H., & Reuner, G. (2019, Mai 8-11). *Entwicklung exekutiver Funktionen 24 Monate nach pädiatrischer Epilepsiechirurgie* [Poster abstract].11. Gemeinsame Jahrestagung der Deutschen und Österreichischen Gesellschaft für Epileptologie sowie der Schweizerischen Epilepsie-Liga. Basel, Schweiz. *Z. Epileptol.* **32** (Suppl 1), 1–62 (2019). https://doi.org/10.1007/s10309-019-0252-z

8. Appendix

Appendix 1: Demographic and epilepsy surgery characteristics of the baseline, 6-months, 1 year, 2 years and 5 years follow-up samples

		Baseline	6-months	1 year	2 years	5 years
Total number of patients		117	104	101	88	35
Sex, male (n%)		63 (53,8)	56 (53,8)	56 (55,4)	44 (50,0)	17 (48,6)
Age at epilepsy onset, year; months, mean (SD)		6;8 (4;6)	6;9 (4;7)	6;7 (4;4)	6;3 (4;3)	5;2 (4;1)
Age at surgery, year; months, mean (SD)		12;10 (3;10)	12;10 (3;10)	12;8 (3;10)	12;6 (3;8)	11;2 (3;10)
Duration of epilepsy until surgery, year; months, mean (SD)		6;2 (4;6)	6;0 (4;7)	6;1 (4;4)	6;2 (4;3)	6;0 (3;6)
Type of resection (%)						
	Lesionectomy	28 (23,9)	26 (25,0)	24 (23,8)	24 (27,3)	9 (25,7)
	Intralobar tailored resection (incl. 1 frontal lobe resection)	37 (31,6)	34 (32,7)	33 (32,7)	28 (31,8)	10 (28,6)
	Multilobar tailored resection	21 (17,9)	17 (16,3)	18 (17,8)	15 (17,0)	7 (20,0)
	AHE	3 (2,6)	2 (1,9)	3 (3,0)	3 (3,4)	2 (5,7)
	Standard temporal resection ± AHE	16 (13,7)	15 (14,4)	13 (12,9)	13 (14,8)	6 (17,1)
	Temporal tailored resection + AHE	12 (10,3)	10 (9,6)	10 (9,9)	5 (5,7)	1 (2,9)
	Standard mulitlobar resection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Localization of surgery, n (%)						
	frontal	35 (29,9)	32 (30,8)	31 (30,7)	27 (30,7)	11 (31,4)
	temporal	50 (42,7)	45 (43,3)	42 (41,6)	37 (42,0)	12 (34,3)
	parietal	7 (6,0)	6 (5,8)	6 (5,9)	5 (5,7)	4 (11,4)
	occipital	3 (2,6)	3 (2,9)	3 (3,0)	3 (3,4)	0 (0)
	insular	1 (0,9)	1 (1,0)	1 (1,0)	1 (1,1)	1 (2,9)
	multilobar	21 (17,9)	17 (16,3)	18 (17,8)	15 (17,0)	7 (20,0)
Side of surgery, n(%)						
	right	64 (54,7)	57 (54,8)	52 (51,5)	45 (51,1)	18 (51,4)
	left	53 (45,3)	47 (45,2)	49 (48,5)	43 (48,9)	17 (48,6)

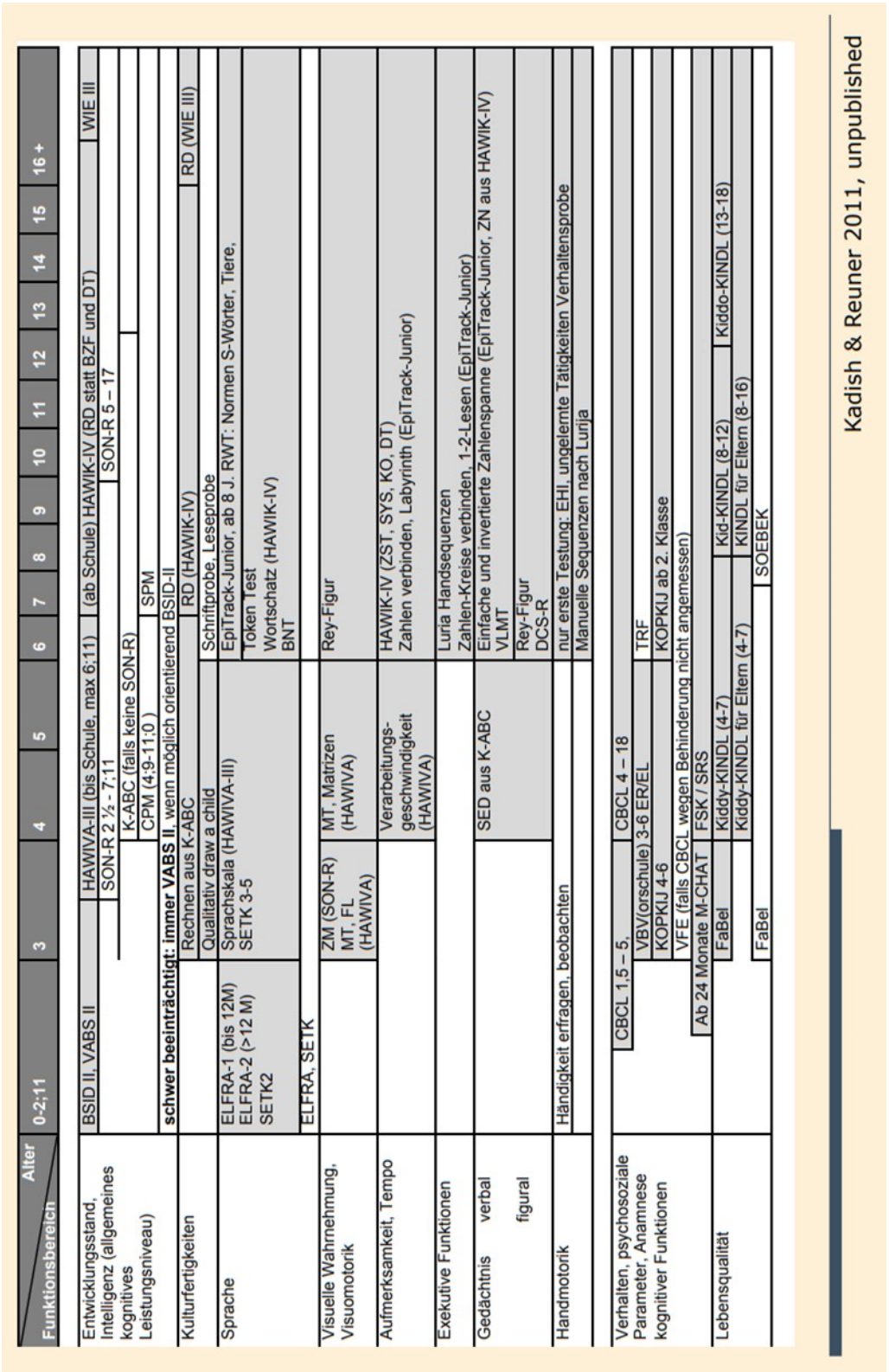
Appendix 1 continuation: Demographic and epilepsy surgery characteristics of the baseline, 6-months, 1 year, 2 years and 5 years follow-up cohorts

Pathology, n (%)						
	MCD	47 (40,2)	41 (39,4)	39 (38,6)	34 (38,6)	17 (48,6)
	Tumor	31 (26,5)	29 (27,9)	26 (25,7)	25 (28,4)	6 (17,1)
	Dual pathology	23 (19,7)	22 (21,2)	22 (21,8)	17 (19,3)	7 (20,0)
	Vascular malformation	2 (1,7)	2 (1,9)	2 (2,0)	1 (1,1)	0 (0)
	Gliosis	8 (6,8)	7 (6,7)	7 (6,9)	6 (6,8)	1 (2,9)
	Mesial temporal sclerosis	5 (4,3)	3 (2,9)	5 (5,0)	5 (5,7)	3 (8,6)
	Other (Vasculitis)	1 (0,9)	0 (0)	0 (0)	0 (0)	1 (2,9)
Type of FCD, n (%)						
	Ia	2 (3,1)	2 (3,4)	2 (3,6)	2 (4,3)	0 (0)
	Ib	8 (12,5)	6 (10,3)	7 (12,7)	6 (13,0)	2 (9,1)
	IIa	17 (26,6)	16 (27,6)	15 (27,3)	12 (26,1)	5 (22,7)
	IIb	7 (10,9)	6 (10,3)	6 (10,9)	6 (13,0)	6 (27,3)
	unknown/before classification	10 (15,6)	9 (15,5)	6 (10,9)	5 (10,9)	3 (13,6)
	FCD+	20 (31,3)	19 (32,8)	19 (34,5)	15 (32,6)	6 (27,3)
	all FCD (n)	64	58	55	46	22
Invasive presurgical EEG, n (%)						
	yes	33 (28,2)	28 (26,9)	30 (29,7)	29 (33,0)	11 (31,4)
	no	76 (65,0)	68 (65,4)	64 (63,4)	53 (60,2)	21 (60,0)
	unknown	8 (6,8)	8 (7,7)	7 (6,9)	6 (6,8)	3 (8,6)

Note. n= Number of patients, AHE= Amygdalohippocampectomy, MCD= Malformation of Cortical Development, FCD= Focal Cortical Dysplasia, FCD+ = dual pathology including a focal cortical dysplasia, EEG = Electroencephalography.

8.2. Appendix 2

Protocol of Perisurgical Neuropsychological Test Battery Used in the University Hospital Heidelberg and in the Epilepsy Center Kork until 2018.



Funktionsbereich \ Alter	0-2;11	3	4	5	6	7	8	9	10	11	12	13	14	15	16 +
Entwicklungsstand, Intelligenz (allgemeines kognitives Leistungsniveau)	BSID II, VABS II		HAWIVA-III (bis Schule, max 6;11)		(ab Schule) HAWIK-IV (RD statt BZF und DT)										WIE III
			SON-R 2 ½ - 7;11								SON-R 5 – 17				
				K-ABC (falls keine SON-R)											
				CPM (4;9-11;0)	SPM										
	schwer beeinträchtigt: immer VABS II, wenn möglich orientierend BSID-II														
Kulturfertigkeiten		Rechnen aus K-ABC			RD (HAWIK-IV)										RD (WIE III)
		Qualitativ draw a child			Schriftprobe, Leseprobe										
Sprache	ELFRA-1 (bis 12M) ELFRA-2 (>12 M) SETK2	Sprachskala (HAWIVA-III) SETK 3-5			EpiTrack-Junior, ab 8 J. RWT: Normen S-Wörter, Tiere, Token Test Wortschatz (HAWIK-IV) BNT										
	ELFRA, SETK														
Visuelle Wahrnehmung, Visuomotorik		ZM (SON-R) MT, FL (HAWIVA)	MT, Matrizen (HAWIVA)		Rey-Figur										
Aufmerksamkeit, Tempo			Verarbeitungs-geschwindigkeit (HAWIVA)		HAWIK-IV (ZST, SYS, KO, DT) Zahlen verbinden, Labyrinth (EpiTrack-Junior)										
Exekutive Funktionen					Luria Handsequenzen Zahlen-Kreise verbinden, 1-2-Lesen (EpiTrack-Junior)										
Gedächtnis verbal			SED aus K-ABC		Einfache und invertierte Zahlenspanne (EpiTrack-Junior, ZN aus HAWIK-IV) VLMT										
figural					Rey-Figur DCS-R										
Handmotorik	Händigkeit erfragen, beobachten				nur erste Testung: EHI, ungelernte Tätigkeiten Verhaltensprobe										
					Manuelle Sequenzen nach Luria										
Verhalten, psychosoziale Parameter, Anamnese kognitiver Funktionen		CBCL 1,5 – 5,	CBCL 4 – 18												
		VBV(orschule) 3-6 ER/EL			TRF										
		KOPKIJ 4-6			KOPKIJ ab 2. Klasse										
		VFE (falls CBCL wegen Behinderung nicht angemessen)													
	Ab 24 Monate M-CHAT	FSK / SRS													
Lebensqualität		FaBel	Kiddy-KINDL (4-7)		Kid-KINDL (8-12)							Kiddo-KINDL (13-18)			
			Kiddy-KINDL für Eltern (4-7)		KINDL für Eltern (8-16)										
		FaBel			SOEBEK										

Kadish & Reuner 2011, unpublished

8.3. Appendix 3

Engel´s Classification of Postoperative Seizure Outcome (Engel et al., 1993)

Class I: Free of disabling seizures [a]

A: Completely seizure free since surgery

B. Nondisabling simple partial seizures only since surgery

C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years

D. Generalized convulsions with AED discontinuation only

Class II: Rare disabling seizures ("almost seizure free")

A. Initially free of disabling seizures but has rare seizures now

B. Rare disabling seizures since surgery

C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years

D. Nocturnal seizures only

Class III: Worthwhile improvement [b]

A. Worthwhile seizure reduction

B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years

Class IV: No worthwhile improvement

A. Significant seizure reduction

B. No appreciable change

C. Seizures worse

Note. *a* Excludes early postoperative seizures (first few weeks). [b] Determination of "worthwhile improvement" will require quantitative analysis of additional data such as percentage of seizure reduction, cognitive function, and quality of life.

8.4. Appendix 4

Analyses of Executive Function Planning

Side of surgery

Table 1: Estimated marginal means in scaled score points and standard errors for each evaluation time and for every side of surgery, in Planning.

Time	Side of surgery	Mean	*SE*
pre	right	8.94	0.37
	left	9.52	0.41
6 mo	right	9.23	0.42
	left	9.76	0.48
12 mo	right	9.47	0.40
	left	9.85	0.42
24 mo	right	9.59	0.42
	left	10.58	0.43
60 mo	right	9.05	0.71
	left	10.33	0.58

Note. Pre = persurgical evaluation, mo = months post-surgery

Table 2: Simple comparisons of Planning scores between both sides of surgery for every evaluation time

Time	Side of surgery comparison	Mean difference	*SE*	*t*	*df*	*p*
pre	right - left	-0.59	0.55	-1.07	186	.29
6 mo	right - left	-0.52	0.64	-0.82	273	.42
12 mo	right - left	-0.37	0.58	-0.64	219	.52
24 mo	right - left	-0.99	0.60	-1.65	238	.10
60 mo	right - left	-1.28	0.92	-1.40	356	.16

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation, mean difference in scaled score points.

Table 3: Pairwise comparisons of Planning scores for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each side of surgery.

Side of surgery	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p*
	pre. - 6 mo	-0.30	.37	-.80	252	.42
	pre - 12 mo	-0.54	.34	-1.56	250	.12
	pre - 24 mo	-0.66	.36	-1.81	252	.07
right	pre - 60 mo	-0.11	.68	-.17	263	.87
	6 mo - 12 mo	-0.24	.40	-.60	255	.55
	12 mo - 24 mo	-0.12	.39	-.31	249	.76
	24 mo - 60 mo	0.54	.71	.77	265	.44
	pre - 6 mo	-0.23	.43	-.54	254	.59
	pre - 12 mo	-0.32	.37	-.89	249	.38
	pre - 24 mo	-1.06	.38	-2.78	252	**.006**
left	pre - 60 mo	-0.81	.54	-1.49	255	.14
	6 mo - 12 mo	-0.09	.45	-.21	257	.84
	12 mo - 24 mo	-0.74	.39	-1.90	248	.059
	24 mo - 60 mo	0.25	.56	.46	253	.65

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Etiology:

Table 4: Estimated marginal means in scaled score points and standard errors for time for each etiology group and for every evaluation time, in Planning:

Time	etiology	*Mean*	*SE*
pre	MCD	9.15	0.42
	tumor	9.32	0.52
	dual pathology	9.43	0.63
	vascular malformation	10.00	2.03
	gliosis	7.88	1.01
	mesial temporal sclerosis	9.40	1.28
	other	11.00	2.86
6 mo	MCD	8.99	0.47
	tumor	10.28	0.63
	dual pathology	10.02	0.71
	vascular malformation	11.50	2.03
	gliosis	6.64	1.57
	mesial temporal sclerosis	8.40	1.66
12 mo	MCD	9.37	0.45
	tumor	10.23	0.56
	dual pathology	9.77	0.66
	vascular malformation	11.85	2.48
	gliosis	7.36	1.10
	mesial temporal sclerosis	10.00	1.28
24 mo	MCD	9.85	0.48
	tumor	11.01	0.56
	dual pathology	9.11	0.68
	vascular malformation	11.85	2.48
	gliosis	8.33	1.10
	mesial temporal sclerosis	11.20	1.28
60 mo	MCD	9.33	0.62
	tumor	11.43	0.95
	dual pathology	8.16	1.20
	gliosis	6.26	2.06
	mesial temporal sclerosis	12.89	2.15
	other	13.00	2.86

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation, MCD = malformation of cortical development

Table 5 : Deviation contrasts in Planning between the mean of the cohort and the etiology groups for every evaluation time in scaled score points.

Time	Etiology Deviation Contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	MCD - Mean	-5.17	3.11	-1.66	159	.10
	tumor - Mean	4.26	3.32	1.28	159	.20
	dual pathology - Mean	-5.51	3.54	-1.56	164	.12
	vascular malformation - Mean	-4.42	8.40	-0.53	156	.60
	gliosis - Mean	-5.92	4.78	-1.24	156	.22
	mesial temporal sclerosis - Mean	1.18	5.69	0.21	156	.84
	Other- Mean	15.58	11.58	1.35	156	.18
6 mo	MCD - Mean	-4.06	3.00	-1.36	226	.18
	tumor - Mean	10.31	3.32	3.10	237	**.002**
	dual pathology - Mean	-3.47	3.58	-0.97	237	.33
	vascular malformation - Mean	-1.48	8.08	-0.18	165	.86
	gliosis - Mean	-3.21	6.11	-0.53	324	.60
	mesial temporal sclerosis - Mean	1.91	6.47	0.30	272	.77
12 mo	MCD - Mean	-5.58	2.93	-1.91	211	.06
	tumor - Mean	10.01	3.15	3.18	205	**.002**
	dual pathology - Mean	-4.89	3.39	-1.44	204	.15
	vascular malformation - Mean	3.57	9.38	0.38	248	.70
	gliosis - Mean	-5.70	4.76	-1.20	200	.23
	mesial temporal sclerosis - Mean	2.58	5.62	0.46	189	.65
24 mo	MCD - Mean	-0.95	2.97	-0.32	219	.75
	tumor - Mean	9.37	3.15	2.98	205	**.003**
	dual pathology - Mean	0.73	3.43	0.21	212	.83
	vascular malformation - Mean	-2.48	9.37	-0.26	248	.79
	gliosis - Mean	-8.65	4.91	-1.76	218	.08
	mesial temporal sclerosis - Mean	1.97	5.43	0.36	170	.72
60 mo	MCD - Mean	-5.84	3.70	-1.58	261	.12
	tumor - Mean	8.52	4.33	1.97	308	.05
	dual pathology - Mean	-4.50	4.59	-0.98	308	.33
	gliosis-Mean	-12.69	7.90	-1.61	354	11
	mesial temporal sclerosis - Mean	3.09	6.22	0.50	225	.62
	Other- Mean	11.42	11.32	1.01	164	32

Note. Mo = months post-surgery, MCD = Malformation of cortical development.

Surgery type:

Table 6: Deviation contrasts in Planning between the mean of the cohort and the different surgical groups for every evaluation time in scaled score points

Time	type of surgery deviation contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	lesionectomy - Mean	0.26	0.58	0.44	185	.66
	intralobar tailored resection - Mean	-1.16	0.53	-2.16	179	**.03**
	multilobar tailored resection - Mean	-0.75	0.63	-1.19	178	.24
	AHE - Mean	1.11	1.40	0.79	178	.43
	standard temporal resection ± AHE - Mean	0.17	0.72	0.23	185	.82
	temporal tailored resection + AHE - Mean	0.38	0.79	0.48	187	.63
6 mo	lesionectomy - Mean	0.94	0.66	1.43	247	.15
	intralobar tailored resection - Mean	-0.88	0.64	-1.38	270	.17
	multilobar tailored resection - Mean	-1.29	0.74	-1.74	261	.08
	AHE - Mean	-0.42	1.56	-0.27	238	.79
	standard temporal resection ± AHE - Mean	0.86	0.84	1.02	268	.31
	temporal tailored resection + AHE - Mean	0.79	1.06	0.74	314	.46
12 mo	lesionectomy - Mean	1.09	0.61	1.80	206	.07
	intralobar tailored resection - Mean	-0.91	0.56	-1.61	205	.11
	multilobar tailored resection - Mean	-0.72	0.69	-1.04	224	.30
	AHE - Mean	0.87	1.41	0.62	179	.54
	standard temporal resection ± AHE - Mean	-0.01	0.76	-0.01	216	.99
	temporal tailored resection + AHE - Mean	-0.34	0.83	-0.41	214	.68
24 mo	lesionectomy - Mean	0.54	0.63	0.87	223	.39
	intralobar tailored resection - Mean	-1.04	0.58	-1.78	224	.08
	multilobar tailored resection - Mean	-1.27	0.71	-1.79	238	.08
	AHE - Mean	1.63	1.41	1.16	180	.25
	standard temporal resection ± AHE - Mean	0.61	0.77	0.79	221	.43
	temporal tailored resection + AHE - Mean	-0.48	0.97	-0.49	290	.63
60 mo	lesionectomy - Mean	-0.15	0.91	-0.16	336	.87
	intralobar tailored resection - Mean	-1.52	0.87	-1.75	337	.08
	multilobar tailored resection - Mean	-1.38	0.93	-1.48	332	.14
	AHE - Mean	3.17	1.88	1.69	325	.09
	standard temporal resection ± AHE - Mean	-0.13	1.06	-0.12	334	.90

Note. time= timing of perisurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy, bold print = significant result

Table 7: Pairwise comparisons of Planning scores in scaled score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgery type group

type of surgery	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
lesionectomy	pre - 6 mo	-0.72	0.54	-1.33	236	.19
	pre - 12 mo	-1.07	0.52	-2.08	235	**.038**
	pre - 24 mo	-1.10	0.54	-2.05	238	**.042**
	pre - 60 mo	-0.52	0.86	-0.61	243	.55
	6 mo - 12 mo	-0.36	0.56	-0.63	234	.53
	12 mo - 24 mo	-0.02	0.55	-0.04	233	.97
	24 mo - 60 mo	0.58	0.87	0.66	240	.51
intralobar tailored resection	pre - 6 mo	-0.31	0.51	-0.60	238	.55
	pre - 12 mo	-0.49	0.44	-1.10	233	.27
	pre - 24 mo	-0.93	0.46	-2.03	234	.04
	pre - 60 mo	-0.56	0.78	-0.72	241	.47
	6 mo - 12 mo	-0.18	0.54	-0.32	241	.75
	12 mo - 24 mo	-0.44	0.49	-0.91	235	.36
	24 mo - 60 mo	0.37	0.81	0.46	242	.65
multilobar tailored resection	pre - 6 mo	0.50	0.66	0.76	238	.45
	pre - 12 mo	-0.27	0.62	-0.43	236	.67
	pre - 24 mo	-0.30	0.64	-0.46	237	.65
	pre - 60 mo	-0.29	0.87	-0.33	242	.74
	6 mo - 12 mo	-0.77	0.73	-1.06	242	.29
	12 mo - 24 mo	-0.03	0.69	-0.04	234	.97
	24 mo - 60 mo	0.01	0.92	0.01	241	.99
AHE	pre - 6 mo	1.49	1.62	-0.90	231	.36
	pre - 12 mo	0.01	1.41	-0.09	227	..99
	pre - 24 mo	-1.33	1.41	-1.71	227	.35
	pre - 60 mo	-2.99	2.13	-0.59	238	.16
	6 mo - 12 mo	-1.49	1.62	0.75	231	.36
	12 mo - 24 mo	-1.33	1.41	-1.60	227	.97
	24 mo - 60 mo	-1.65	2.13	0.56	238	.99
standard temporal resection ± AHE	pre - 6 mo	-0.72	0.80	-0.90	236	.36
	pre - 12 mo	-0.07	0.73	-0.09	239	.99
	pre - 24 mo	-1.25	0.73	-1.71	239	.35
	pre - 60 mo	-0.63	1.06	-0.59	242	.16
	6 mo - 12 mo	0.66	0.88	0.75	250	.36
	12 mo - 24 mo	-1.18	0.74	-1.60	227	.35
	24 mo - 60 mo	0.62	1.11	0.56	248	.44
temporal tailored resection + AHE	pre - 6 mo	-0.44	1.15	-0.39	262	.37
	pre - 12 mo	0.48	0.80	0.60	235	.93
	pre - 24 mo	0.05	1.03	0.05	253	.09

6 mo - 12 mo	0.92	1.15	0.77	265	.46
12 mo - 24 mo	-0.44	1.05	-0.42	248	.11

Note. Pre = presurgical evaluation, mo = month8s post-surgery, AHE = amygdalohippocampectomy

Localization:

Table 8 : Deviation contrasts in Planning between the mean of the cohort and the different localization groups for every evaluation time in scaled score points

Time	Localization Deviation Contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	frontal - Mean	-0.64	0.72	-0.89	182	.37
	temporal - Mean	1.20	0.68	1.75	181	.08
	parietal - Mean	0.37	1.06	0.35	179	.73
	occipital - Mean	-0.91	1.47	-0.62	179	.54
	insular - Mean	0.09	2.40	0.04	179	.97
	multilobar - Mean	-0.10	0.78	-0.13	179	.90
6 mo	frontal - Mean	-1.03	0.76	-1.35	214	.18
	temporal - Mean	1.08	0.76	1.42	238	.16
	parietal - Mean	0.78	1.15	0.68	221	.50
	occipital - Mean	-0.94	1.62	-0.58	233	.56
	multilobar - Mean	-1.29	0.86	-1.50	231	.14
12 mo	frontal - Mean	-1.47	0.74	-1.99	195	.05
	temporal - Mean	0.15	0.70	0.21	195	.83
	parietal - Mean	0.74	1.14	0.64	216	.52
	occipital - Mean	-1.17	1.48	-0.79	181	.43
	insular - Mean	2.83	2.41	1.18	180	.24
	multilobar - Mean	-1.09	0.83	-1.31	211	.19
24 mo	frontal - Mean	-0.61	0.62	-0.98	223	.33
	temporal - Mean	0.61	0.58	1.06	221	.29
	parietal - Mean	0.40	1.08	0.37	253	.71
	occipital - Mean	0.58	1.36	0.43	183	.67
	multilobar - M	-0.98	0.72	-1.37	235	.17
60 mo	frontal - Mean	-0.92	0.72	-1.29	334	.20
	temporal - Mean	1.27	0.82	1.54	335	.12
	parietal - Mean	0.35	1.02	0.34	279	.73
	multilobar - Mean	-0.69	0.82	-0.85	332	.40

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Table 9: Estimated marginal means in scaled score points and standard errors for time for each localization group and for every evaluation time, in Planning

Time	localization	Mean	*SE*
pre	frontal	8.27	0.49
	temporal	10.11	0.41
	parietal	9.29	1.08
	occipital	8.00	1.65
	insular	9.00	2.85
	multilobar	8.81	0.62
6 mo	frontal	8.58	0.53
	temporal	10.68	0.54
	parietal	10.38	1.19
	occipital	8.66	1.83
	insular	11.00	2.85
	multilobar	8.31	0.73
12 mo	frontal	8.70	0.51
	temporal	10.32	0.44
	parietal	10.90	1.19
	occipital	9.00	1.65
	insular	13.00	2.85
	multilobar	9.08	0.70
24 mo	frontal	9.48	0.53
	temporal	10.70	0.45
	parietal	10.49	1.26
	occipital	10.67	1.65
	multilobar	9.10	0.71
60 mo	frontal	8.87	0.74
	temporal	11.06	0.93
	parietal	10.14	1.26
	multilobar	9.10	0.92

Note. Pre = persurgical evaluation, mo = months post-surgery

Table 10: Pairwise comparisons of Planning scores for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgical localization.

localization	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p*
	pre - 6 mo	-0.30	0.48	-0.63	237	.53
	pre - 12 mo	-0.43	0.46	-0.94	236	.35
	pre - 24 mo	-1.21	0.48	-2.50	239	**.013**
frontal	pre - 60 mo	-0.60	0.71	-0.84	244	.40
	6 mo - 12 mo	-0.13	0.50	-0.25	239	.80
	12 mo - 24 mo	-0.78	0.50	-1.57	237	.12
	24 mo - 60 mo	0.62	0.73	0.84	242	.40
	pre - 6 mo	-0.57	0.50	-1.15	247	.25
	pre - 12 mo	-0.21	0.39	-0.54	238	.59
	pre - 24 mo	-0.59	0.41	-1.46	240	.15
temporal	pre - 60 mo	-0.95	0.91	-1.05	251	.30
	6 mo - 12 mo	0.36	0.53	0.69	253	.49
	12 mo - 24 mo	-0.38	0.42	-0.91	236	.37
	24 mo - 60 mo	-0.36	0.92	-0.39	251	.70
	pre - 6 mo	-1.10	1.05	-1.04	240	.30
	pre - 12 mo	-1.62	1.05	-1.54	240	.13
	pre - 24 mo	-1.20	1.14	-1.06	241	.29
parietal	pre - 60 mo	-0.85	1.14	-0.75	241	.45
	6 mo - 12 mo	-0.52	1.13	-0.46	235	.64
	12 mo - 24 mo	0.41	1.22	0.34	239	.73
	24 mo - 60 mo	0.35	1.27	0.27	237	.78
	pre - 6 mo	-0.66	1.62	-0.41	234	.68
	pre - 12 mo	-1.00	1.41	-0.71	229	.48
occipital	pre - 24 mo	-2.67	1.41	-1.89	229	.060
	6 mo - 12 mo	-0.34	1.62	-0.24	234	.84
	12 mo - 24 mo	-1.67	1.41	-1.18	229	.24
	pre - 6 mo	-2.00	2.45	-0.82	229	.41
insular	pre - 12 mo	-4.00	2.45	-1.64	229	.10
	6 mo - 12 mo	-2.00	2.45	-0.82	229	.41
	pre - 6 mo	0.50	0.66	0.76	240	.45
	pre - 12 mo	-0.27	0.62	-0.43	239	.67
	pre - 24 mo	-0.30	0.64	-0.46	240	.64
multilobar	pre - 60 mo	-0.29	0.87	-0.33	245	.74
	6 mo - 12 mo	-0.77	0.73	-1.06	245	.29
	12 mo - 24 mo	-0.03	0.69	-0.04	237	.97
	24 mo - 60 mo	0.01	0.92	0.01	244	.99

Note. Pre = presurgical evaluation, mo = months post-surgery

Seizure outcome:

Table F: Estimated marginal means in scaled score points and standard errors for time for each seizure outcome group (in Engel categories) and for every evaluation time, in Planning

Time	Engel	*Mean*	*SE*
pre	/	9.20	0.27
6 mo	1a	9.74	0.35
	> 1a	8.65	0.55
12 mo	1a	9.86	0.33
	> 1a	9.28	0.43
24 mo	1a	10.23	0.35
	> 1a	9.96	0.42
60 mo	1a	9.88	0.60
	> 1a	9.86	0.61

Note. Pre = presurgical evaluation, mo = months post-surgery

Antiseizure drug load:

Table G: Estimated marginal means in scaled score points and standard errors for time for each antiseizure drug load group and for every evaluation time, in Planning

Time	ASM	*Mean*	*SE*
pre	0	8.76	1.45
	1	9.12	0.41
	> 1	9.24	0.30
6 mo	1	9.64	0.39
	> 1	9.25	0.41
12 mo	0	10.25	0.88
	1	9.97	0.34
	> 1	9.25	0.40
24 mo	0	10.45	0.47
	1	10.59	0.38
	> 1	9.16	0.47
60 mo	0	10.07	0.93
	1	10.74	0.63
	> 1	8.67	0.71

Note. Pre = presurgical evaluation, mo = months post-surgery, ASM = antiseizure medication load

8.5. Appendix 5:

Analyses of Executive Function Problem Solving

Side of surgery :

Table 1: Estimated marginal means in scaled score points and standard errors for each evaluation time and for every side of surgery, in Problem Solving.

Time	Side of surgery	Mean	*SE*
pre	right	8.90	0.43
	left	10.04	0.48
6 mo	right	9.00	0.51
	left	10.44	0.63
12 mo	right	8.46	0.49
	left	9.51	0.50
24 mo	right	8.90	0.50
	left	10.28	0.53
60 mo	right	7.82	0.73
	left	9.52	0.84

Note. Pre = persurgical evaluation, mo = months post-surgery

Table 2: Pairwise comparisons of Planning in scaled score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each side of surgery.

Side of surgery	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p.*
right	pre - 6 mo	-0.10	0.49	-0.21	196	.84
	pre - 12 mo	0.43	0.47	0.92	198	.36
	pre - 24 mo	0.01	0.48	0.01	195	.99
	pre - 60 mo	1.08	0.72	1.50	209	.14
	6 mo - 12 mo	0.54	0.53	1.00	198	.32
	12 mo - 24 mo	-0.43	0.52	-0.83	195	.41
	24 mo - 60 mo	1.08	0.75	1.43	207	.16
left	pre - 6 mo	-0.39	0.61	-0.64	198	.52
	pre - 12 mo	0.54	0.49	1.09	196	.28
	pre - 24 mo	-0.24	0.52	-0.45	197	.65
	pre - 60 mo	0.52	0.83	0.63	205	.53
	6 mo - 12 mo	0.93	0.63	1.47	199	.14
	12 mo - 24 mo	-0.77	0.53	-1.45	193	.15
	24 mo - 60 mo	0.75	0.86	0.88	205	.38

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Etiology:

Table 3: Estimated marginal means in scaled score points and standard errors for time for each etiology group and for every evaluation time, in Planning

Time	etiology	*Mean*	*SE*
pre	MCD	8.88	0.51
	tumor	10.62	0.60
	dual pathology	9.21	0.65
	vascular malformation	11.00	2.14
	gliosis	9.60	1.21
	mesial temporal sclerosis	5.94	1.68
6 mo	MCD	8.64	0.58
	tumor	10.79	0.82
	dual pathology	9.80	0.81
	vascular malformation	12.00	2.14
	gliosis	9.91	1.78
	mesial temporal sclerosis	6.59	2.43
12 mo	MCD	7.47	0.54
	tumor	10.92	0.68
	dual pathology	8.63	0.71
	vascular malformation	12.43	2.68
	gliosis	9.72	1.28
	mesial temporal sclerosis	9.17	1.91
24 mo	MCD	8.45	0.58
	tumor	10.91	0.68
	dual pathology	9.33	0.73
	vascular malformation	10.43	2.68
	gliosis	8.27	1.53
	mesial temporal sclerosis	10.94	1.68
60 mo	MCD	6.86	0.73
	tumor	9.54	1.35
	dual pathology	9.90	1.35
	mesial temporal sclerosis	10.75	1.65

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation, MCD = malformation of cortical development

Table 4 : Deviation contrasts in Problem Solving between the mean of the cohort and the etiology groups for every evaluation time in scaled score points.

Time	Etiology Deviation Contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	MCD - Mean	-0.33	0.67	-0.49	169	.63
	tumor - Mean	1.41	0.72	1.96	164	.05
	dual pathology - Mean	0.01	0.75	0.01	164	.99
	vascular malformation - Mean	1.79	1.82	0.98	156	.33
	gliosis - Mean	0.39	1.12	0.35	172	.73
	mesial temporal sclerosis - Mean	-3.27	1.47	-2.23	185	**.027**
6 mo	MCD - Mean	-0.98	0.81	-1.21	237	.23
	tumor - Mean	1.17	0.93	1.25	250	.21
	dual pathology - Mean	0.18	0.93	0.19	240	.85
	vascular malformation - Mean	2.38	1.86	1.28	166	.20
	gliosis - Mean	0.29	1.59	0.18	260	.86
	mesial temporal sclerosis - Mean	-3.03	2.09	-1.45	261	.15
12 mo	MCD - Mean	-2.25	0.76	-2.97	216	**.003**
	tumor - Mean	1.20	0.83	1.45	219	.15
	dual pathology - Mean	-1.09	0.85	-1.29	212	.20
	vascular malformation - Mean	2.71	2.28	1.19	235	.24
	gliosis - Mean	-0.003	1.21	-0.003	204	.99
	mesial temporal sclerosis - Mean	-0.55	1.68	-0.33	232	.74
24 mo	MCD - Mean	-1.27	0.78	-1.63	224	.11
	tumor - Mean	1.19	0.83	1.44	218	.15
	dual pathology - Mean	-0.39	0.86	-0.46	215	.65
	vascular malformation - Mean	0.71	2.28	0.31	235	.76
	gliosis - Mean	-1.46	1.39	-1.04	242	.30
	mesial temporal sclerosis - Mean	1.22	1.50	0.81	195	.42
60 mo	MCD - Mean	-2.40	0.83	-2.88	260	**.004**
	tumor - Mean	0.27	1.16	0.23	251	.82
	dual pathology - Mean	0.64	1.16	0.55	254	.58
	mesial temporal sclerosis - Mean	1.49	1.34	1.11	212	.27

Note. Mo = months post-surgery, MCD = Malformation of cortical development.

Table 5 : Pairwise comparisons of Problem Solving scores for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each etiology group.

etiology	Time Pairwise Contrasts	Mean difference	*SE*	*t*	*df*	*p*
	pre - 6 mo	0.24	0.57	0.42	181	.67
	pre - 12 mo	1.41	0.53	2.67	184	**.008**
	pre - 24 mo	0.43	0.57	0.75	182	.45
MCD	pre - 60 mo	2.02	0.71	2.84	184	**.005**
	6 mo - 12 mo	1.17	0.58	2.02	179	**.045**
	12 mo - 24 mo	-0.98	0.58	-1.70	177	.09
	24 mo - 60 mo	1.59	0.75	2.11	183	**.036**
	pre - 6 mo	-0.17	0.79	-0.22	184	.83
	pre - 12 mo	-0.31	0.64	-0.48	179	.63
	pre - 24 mo	-0.30	0.64	-0.46	179	.65
tumor	pre - 60 mo	1.08	1.33	0.81	188	.42
	6 mo - 12 mo	-0.14	0.86	-0.16	191	.88
	12 mo - 24 mo	0.01	0.71	0.02	182	.99
	24 mo - 60 mo	1.38	1.37	1.01	188	.32
	pre - 6 mo	-0.58	0.77	-0.76	180	.45
	pre - 12 mo	0.58	0.68	0.87	179	.39
	pre - 24 mo	-0.11	0.69	-0.16	180	.87
dual pathology	pre - 60 mo	-0.69	1.33	-0.52	185	.60
	6 mo - 12 mo	1.17	0.82	1.42	183	.16
	12 mo - 24 mo	-0.70	0.72	-0.97	175	.34
	24 mo - 60 mo	-0.58	1.37	-0.42	186	.67
	pre - 6 mo	-1.00	1.96	-0.51	169	.61
	pre - 12 mo	-1.43	2.54	-0.56	181	.58
vascular malformation	pre - 24 mo	0.57	2.54	0.23	181	.82
	6 mo - 12 mo	-0.43	2.54	-0.17	181	.87
	12 mo - 24 mo	2.00	2.77	0.72	169	.47
	pre - 6 mo	-0.31	1.73	-0.18	187	.86
	pre - 12 mo	-0.12	1.28	-0.10	197	.92
gliosis	pre - 24 mo	1.33	1.47	0.90	185	.37
	6 mo - 12 mo	0.19	1.76	0.11	185	.92
	12 mo - 24 mo	1.46	1.59	0.92	198	.36
	pre - 6 mo	-0.65	2.39	-0.27	177	.79
	pre - 12 mo	-3.23	1.84	-1.76	174	.08
	pre - 24 mo	-5.00	1.60	-3.13	169	**.002**
mesial temporal sclerosis	pre - 60 mo	-4.81	1.74	-2.76	200	**.006**
	6 mo - 12 mo	-2.58	2.50	-1.03	175	.30
	12 mo - 24 mo	-1.77	1.84	-0.96	174	.34
	24 mo - 60 mo	0.19	1.74	0.11	200	.91

Surgery type:

Table 6: Estimated marginal means in scaled score points and standard errors for time for each surgery type group and for every evaluation time, in Problem Solving

Time	type of surgery	*Mean*	*SE*
Pre	lesionectomy	10.04	0.63
	intralobar tailored resection	8.97	0.58
	multilobar tailored resection	8.89	0.72
	AHE	6.50	2.17
	standard temporal resection ± AHE	10.65	0.89
	temporal tailored resection + AHE	9.64	0.99
6 mo	lesionectomy	10.33	0.74
	intralobar tailored resection	9.48	0.76
	multilobar tailored resection	9.10	0.91
	AHE	7.48	2.69
	standard temporal resection ± AHE	10.42	0.99
	temporal tailored resection + AHE	8.90	1.33
12 mo	lesionectomy	10.25	0.68
	intralobar tailored resection	8.01	0.62
	multilobar tailored resection	8.89	0.82
	AHE	9.48	2.69
	standard temporal resection ± AHE	9.52	0.92
	temporal tailored resection + AHE	7.62	1.15
24 mo	lesionectomy	10.44	0.66
	intralobar tailored resection	8.70	0.69
	multilobar tailored resection	8.47	0.87
	AHE	12.50	2.17
	standard temporal resection ± AHE	10.84	0.89
	temporal tailored resection + AHE	6.17	1.79
60 mo	lesionectomy	8.69	0.95
	intralobar tailored resection	8.41	1.22
	multilobar tailored resection	7.26	1.23
	AHE	12.50	2.17
	standard temporal resection ± AHE	9.18	1.42
	temporal tailored resection + AHE	7.00	3.07

Note. AHE = amygdalohippocampectomy, mo = months post-surgery, pre = presurgical evaluation

Table 7: Deviation contrasts in Problem solving between the mean of the cohort and the different surgical groups for every evaluation time in scaled score points

Time	type of surgery deviation contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	lesionectomy - Mean	0.92	0.70	1.33	158	.19
	intralobar tailored resection - Mean	-0.14	0.66	-0.21	161	.83
	multilobar tailored resection - Mean	-0.23	0.75	-0.30	154	.76
	AHE - Mean	-2.62	1.83	-1.43	153	.16
	standard temporal resection ± AHE - Mean	1.53	0.87	1.77	168	.08
	temporal tailored resection + AHE - Mean	0.53	0.93	0.56	171	.57
6 mo	lesionectomy - Mean	1.04	0.83	1.25	227	.21
	intralobar tailored resection - Mean	0.20	0.85	0.23	244	.82
	multilobar tailored resection - Mean	-0.18	0.94	-0.20	234	.85
	AHE - Mean	-1.81	2.27	-0.80	234	.43
	standard temporal resection ± AHE - Mean	1.13	0.99	1.15	220	.25
	temporal tailored resection + AHE - Mean	-0.38	1.23	-0.31	249	.76
12 mo	lesionectomy - Mean	1.29	0.78	1.64	206	.10
	intralobar tailored resection - Mean	-0.95	0.75	-1.28	209	.20
	multilobar tailored resection - Mean	-0.07	0.87	-0.09	211	.93
	AHE - Mean	0.52	2.26	0.23	234	.82
	standard temporal resection ± AHE - Mean	0.56	0.93	0.60	199	.55
	temporal tailored resection + AHE - Mean	-1.34	1.09	-1.23	219	.22
24 mo	lesionectomy - Mean	0.92	0.76	1.21	192	.23
	intralobar tailored resection - Mean	-0.82	0.78	-1.06	219	.29
	multilobar tailored resection - Mean	-1.05	0.89	-1.18	218	.24
	AHE - Mean	2.98	1.85	1.61	157	.11
	standard temporal resection ± AHE - Mean	1.32	0.91	1.46	186	.15
	temporal tailored resection + AHE - Mean	-3.35	1.56	-2.16	259	**.032**
60 mo	lesionectomy - Mean	-0.15	1.08	-0.14	241	.89
	intralobar tailored resection - Mean	-0.43	1.24	-0.35	259	.73
	multilobar tailored resection - Mean	-1.58	1.25	-1.26	255	.21
	AHE - Mean	3.66	1.92	1.90	159	.06
	standard temporal resection ± AHE - Mean	0.34	1.38	0.24	257	.81
	temporal tailored resection + AHE - Mean	-1.84	2.62	-0.70	156	.48

Note. time= timing of perisurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy, bold print = significant result

Table 8: Pairwise comparisons of Problem Solving scores in scaled score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgery type group

type of surgery	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
lesionectomy	pre - 6 mo	-0.29	0.70	-0.42	174	.68
	pre - 12 mo	-0.21	0.65	-0.33	174	.74
	pre - 24 mo	-0.41	0.62	-0.62	173	.52
	pre - 60 mo	1.34	0.92	1.47	178	.15
	6 mo - 12 mo	0.08	0.74	0.11	173	.91
	12 mo - 24 mo	-0.20	0.66	-0.30	170	.77
	24 mo - 60 mo	1.75	0.94	1.87	177	.06
intralobar tailored resection	pre - 6 mo	-0.51	0.74	-0.69	183	.49
	pre - 12 mo	0.97	0.60	1.62	179	.11
	pre - 24 mo	0.28	0.66	0.42	178	.68
	pre - 60 mo	0.56	1.21	0.47	194	.64
	6 mo - 12 mo	1.48	0.77	-1.93	183	.06
	12 mo - 24 mo	-0.69	0.70	-0.99	183	.33
	24 mo - 60 mo	0.29	1.26	0.23	195	.82
multilobar tailored resection	pre - 6 mo	-0.22	0.86	-0.25	178	.80
	pre - 12 mo	0.01	0.77	0.01	175	.99
	pre - 24 mo	0.42	0.82	0.51	177	.61
	pre - 60 mo	1.63	1.20	1.36	183	.18
	6 mo - 12 mo	0.22	0.93	0.23	179	.82
	12 mo - 24 mo	0.42	0.89	0.47	177	.64
	24 mo - 60 mo	1.21	1.28	0.94	184	.35
AHE	pre - 6 mo	-0.98	2.54	-0.39	173	.70
	pre - 12 mo	-2.98	2.54	-0.17	173	.24
	pre - 24 mo	-6.00	2.00	-3.02	166	**.003**
	pre - 60 mo	-6.00	2.00	-3.02	166	**.003**
	6 mo - 12 mo	-2.00	2.81	-0.71	166	.48
	12 mo - 24 mo	-3.02	2.54	-1.19	173	.24
	24 mo - 60 mo	0.01	2.00	0.01	166	0.99
standard temporal resection ± AHE	pre - 6 mo	0.23	0.96	0.24	173	.81
	pre - 12 mo	1.13	0.90	1.25	175	.21
	pre - 24 mo	-0.20	0.88	-0.22	173	.82
	pre - 60 mo	1.47	1.39	1.06	178	.29
	6 mo - 12 mo	0.90	1.02	0.89	182	.38
	12 mo - 24 mo	-1.33	0.87	1.52	167	.13
	24 mo - 60 mo	1.67	1.42	1.17	183	.24
	pre - 6 mo	0.74	1.30	0.57	191	.57

temporal tailored resection + AHE	pre - 12 mo	2.02	1.20	1.69	218	.09
	pre - 24 mo	3.48	1.84	1.89	215	.06
	6 mo - 12 mo	1.28	1.47	0.87	208	.38
	12 mo - 24 mo	1.46	1.78	0.82	190	.41

Note. Pre = presurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy

Localization of surgery:

Table 9: Estimated marginal means in scaled score points and standard errors for time for each localization group and for every evaluation time, in Problem Solving

Time	localization	*Mean*	*SE*
pre	frontal	8.73	.59
	temporal	9.89	.49
	parietal	10.00	1.33
	occipital	10.33	1.78
	insular	12.00	3.07
	multilobar	8.89	.73
6 mo	frontal	9.10	.67
	temporal	9.96	.64
	parietal	10.84	1.58
	occipital	10.90	2.00
	multilobar	9.10	.91
12 mo	frontal	7.89	.64
	temporal	9.08	.54
	parietal	12.55	1.34
	occipital	10.33	1.78
	insular	7.00	3.07
	multilobar	8.89	.82
24 mo	frontal	8.39	.65
	temporal	10.31	.55
	parietal	14.96	1.81
	occipital	10.67	1.78
	insular	6.00	3.07
	multilobar	8.47	.87
60 mo	frontal	7.50	.99
	temporal	10.11	.99
	parietal	9.87	1.58
	insular	10.00	3.07
	multilobar	7.27	1.23

Note. pre = presurgical evaluation, mo = months post-surgery

Table 10 : Deviation contrasts in Problem Solving between the mean of the cohort and the different localization groups for every evaluation time in scaled score points

Time	Localization Deviation Contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	frontal - Mean	-1.24	0.81	-1.53	160	.13
	temporal - Mean	-0.09	0.77	-0.11	159	.91
	parietal - Mean	0.03	1.27	0.02	170	.98
	occipital - Mean	0.36	1.59	0.23	154	.82
	insular - Mean	2.03	2.59	0.78	153	.44
	multilobar - Mean	-1.09	0.88	-1.23	155	.22
6 mo	frontal - Mean	-0.88	0.77	-1.14	219	.26
	temporal - Mean	-0.02	0.76	-0.03	234	.98
	parietal - Mean	0.86	1.35	0.64	230	.52
	occipital - Mean	0.92	1.65	0.56	206	.58
	multilobar - Mean	-0.88	0.90	-0.97	229	.33
12 mo	frontal - Mean	-1.47	0.84	-1.66	174	.10
	temporal - Mean	-0.21	0.80	-0.26	172	.79
	parietal - Mean	3.26	1.28	2.56	170	**.011**
	occipital - Mean	1.04	1.59	0.66	154	.51
	insular - Mean	-2.29	2.60	-0.88	154	.38
	multilobar - Mean	-0.41	0.94	-0.43	181	.67
24 mo	frontal - Mean	-1.41	0.87	-1.62	190	.11
	temporal - Mean	0.51	0.83	0.62	190	.54
	parietal - Mean	5.16	1.64	3.16	251	**.002**
	occipital - Mean	0.87	1.61	0.54	158	.59
	multilobar - M	-1.33	1.00	-1.34	203	.15
60 mo	frontal - Mean	-1.45	1.07	-1.36	244	.18
	temporal - Mean	1.16	1.10	1.06	253	.29
	parietal - Mean	0.92	1.45	0.64	225	.53
	insular- Mean	1.05	2.51	0.42	157	.68
	multilobar - Mean	-1.68	1.23	-1.36	255	.17

Table 11: Pairwise comparisons of Problem Solving scores in scaled scores points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgical localization subgroup.

Localization	Time Pairwise Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
frontal	pre - 6 mo	-0.37	0.64	-0.57	175	.57
	pre - 12 mo	0.84	0.62	1.36	181	.18
	pre - 24 mo	0.32	0.62	0.55	177	.58
	pre - 60 mo	1.24	0.92	1.34	185	.18
	6 mo - 12 mo	1.21	0.69	1.76	179	.08
	12 mo - 24 mo	-0.50	0.67	-0.75	179	.46
	24 mo - 60 mo	0.89	0.96	0.93	185	.35
temporal	pre - 6 mo	-0.07	0.62	-0.11	183	.91
	pre - 12 mo	0.81	0.52	1.54	183	.12
	pre - 24 mo	-0.42	0.54	-0.79	181	.43
	pre - 60 mo	-0.22	1.00	-0.22	205	.83
	6 mo - 12 mo	0.88	0.67	1.32	188	.19
	12 mo - 24 mo	-1.23	0.56	-2.19	177	**.030**
	24 mo - 60 mo	0.20	1.02	0.20	203	.84
parietal	pre - 6 mo	-0.84	1.60	-0.53	195	.60
	pre - 12 mo	-2.55	1.32	-1.93	186	.06
	pre - 24 mo	-4.96	1.77	-2.81	181	**.006**
	pre - 60 mo	0.13	1.52	0.09	180	.93
	6 mo - 12 mo	-1.71	1.50	-1.14	175	.26
	12 mo - 24 mo	-2.41	1.76	-1.37	178	.17
	24 mo - 60 mo	5.09	1.86	2.74	171	**.007**
occipital	pre - 6 mo	-0.57	1.86	-0.30	172	.76
	pre - 12 mo	0.001	1.62	0.001	167	.99
	pre - 24 mo	-0.33	1.62	-0.21	167	.84
	6 mo - 12 mo	0.57	1.86	0.30	172	.76
	12 mo - 24 mo	-0.33	1.62	-0.21	167	.84
insular	pre - 12 mo	5.00	2.80	1.78	167	.08
	pre - 24 mo	6.00	2.80	2.14	167	**.034**
	pre - 60 mo	2.00	2.80	0.71	167	.48
	12 mo - 24 mo	1.00	2.80	0.36	167	.72
	24 mo - 60 mo	-4.00	2.80	-1.43	167	.16
multilobar	pre - 6 mo	-0.22	0.86	-0.25	180	.80
	pre - 12 mo	0.004	0.77	0.01	176	.99
	pre - 24 mo	0.42	0.82	0.52	178	.61
	pre - 60 mo	1.62	1.20	1.36	184	.18
	6 mo - 12 mo	0.22	0.93	0.24	180	.81

	12 mo - 24 mo	0.42	0.89	0.47	178	.64
	24 mo - 60 mo	1.20	1.28	0.94	185	.35

Note. Pre = presurgical evaluation, mo = months post-surgery

Seizure outcome :

Table 12: Estimated marginal means in scaled score points and standard errors for time for each seizure outcome group (in Engel categories) and for every evaluation time, in Problem Solving

Time	Engel	*Mean*	*SE*
pre	/	9.42	0.33
6 mo	1a	9.80	0.44
	> 1a	9.25	0.78
12 mo	1a	8.98	0.40
	> 1a	8.99	0.59
24 mo	1a	9.27	0.44
	> 1a	9.80	0.56
60 mo	1a	9.12	0.73
	> 1a	8.19	0.81

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 13: Pairwise Comparisons of Problem Solving scores between both seizure outcome groups for every post-surgical evaluation time:

Time	Engel outcome Pairwise Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
6 mo	1a - > 1a	0.55	0.85	0.64	220	.52
12 mo	1a - > 1a	-0.01	0.66	-0.01	231	.99
24 mo	1a - > 1a	-0.53	0.66	-0.80	226	.43
60 mo	1a - > 1a	0.93	1.06	0.88	214	.38

Note. mo = months post-surgery

Tableau 14 : Pairwise comparisons of Problem Solving scores between consecutive evaluations for each Seizure outcome group

Engel outcome	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
1a	6 mo - 12 mo	0.82	0.47	1.74	190	.08
	12 mo - 24 mo	-0.29	0.46	-0,64	187	.52
	24 mo - 60 mo	0.15	0.77	0.20	202	.84
>1a	6 mo - 12 mo	0.27	0.88	0.30	204	.76
	12 mo - 24 mo	-0.81	0.70	-1.16	202	.25
	24 mo - 60 mo	1.61	0.89	1.82	199	.07

Antiseizure drug load:

Table 15: Estimated marginal means in scaled score points and standard errors for time for each antiseizure drug load group and for every evaluation time, in Problem Solving

Time	ASM	*Mean*	*SE*
pre	0	7.92	1.77
	1	9.56	0.52
	> 1	9.42	0.37
6 mo	1	9.83	0.53
	> 1	9.41	0.54
12 mo	0	8.09	1.21
	1	9.23	0.46
	> 1	8.78	0.51
24 mo	0	10.05	0.62
	1	9.31	0.50
	> 1	9.07	0.64
60 mo	0	8.59	1.10
	1	8.97	0.80
	> 1	8.36	0.99

Note. ASM = number of antiseizure medications, mo = months post-surgery, pre = presurgical evaluation

Table 16 : Pairwise comparisons of Problem Solving in scaled scores between the Antiseizure drug load groups (ASM) for each evaluation time.

Time	ASM Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
pre	0 - 1	-1.64	1.82	-0.90	231	.37
	0 - > 1	-1.50	1.79	-0.84	233	.40
	1 - > 1	0.14	0.58	0.24	236	.81
6 mo	1 - > 1	0.42	0.71	0.59	226	.55
12 mo	0 - 1	-1.13	1.25	-0.91	208	.37
	0 - > 1	-0.69	1.28	-0.53	217	.59
	1 - > 1	0.45	0.63	0.71	238	.48
24 mo	0 - 1	0.75	0.74	1.01	214	.32
	0 - > 1	0.98	0.86	1.14	232	.26
	1 - > 1	0.23	0.76	0.31	221	.76
60 mo	0 - 1	-0.38	1.32	-0.28	215	.78
	0 - > 1	0.24	1.46	0.16	222	.87
	1 - > 1	0.61	1.24	0.49	207	.62

Note. mo = months post-surgery, pre = presurgical evaluation, ASM = number of antiseizure medications

8.6. Appendix 6

Analyses of Executive Function Fluency

Side of surgery :

Table 1: Estimated marginal means in z-scores and standard errors for each evaluation time and for every side of surgery, in Fluency

Time	Side of surgery	Mean	*SE*
pre	right	0.86	0.18
	left	0.71	0.19
6 mo	right	0.73	0.19
	left	0.30	0.19
12 mo	right	0.44	0.21
	left	0.23	0.19
24 mo	right	0.79	0.20
	left	0.13	0.19
60 mo	right	0.54	0.38
	left	0.24	0.27

Note. Pre = persurgical evaluation, mo = months post-surgery

Table 2 : Simple comparisons for Fluency in z-scores, comparing both surgery groups for every evaluation time.

Time	Side of surgery Simple Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
pre.	right - left	-0.15	0.26	-0.58	170	.57
6 mo	right - left	-0.43	0.26	-1.63	180	.10
12 mo	right - left	-0.21	0.28	-0.75	206	.46
24 mo	right - left	-0.66	0.28	-2.39	199	**.018**
60 mo	right - left	-0.78	0.47	-1.66	235	.10

Note. pre = presurgical evaluation, mo = months post-surgery

Table 3: Pairwise comparisons of Fluency scores in z-score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each side of surgery.

Side of surgery	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
	pre - 6 mo	-0.13	0.18	-0.72	153	.47
	pre - 12 mo	-0.42	0.21	-2.02	159	**.045**
	pre - 24 mo	-0.07	0.19	-0.34	158	.74
right	pre - 60 mo	-0.32	0.39	-0.82	223	.41
	6 mo - 12 mo	-0.29	0.22	-1.34	162	.18
	12 mo - 24 mo	0.35	0.22	1.59	158	.11
	24 mo - 60 mo	-0.25	0.41	-0.63	223	.53
	pre - 6 mo	-0.41	0.19	-2.20	154	**.030**
	pre - 12 mo	-0.48	0.19	-2.50	159	**.013**
	pre - 24 mo	-0.58	0.20	-2.90	160	**.004**
left	pre - 60 mo	-0.95	0.30	-3.21	216	**.002**
	6 mo - 12 mo	-0.07	0.19	-0.38	159	.71
	12 mo - 24 mo	-0.10	0.20	-0.49	155	.63
	24 mo - 60 mo	-0.37	0.29	-1.25	209	.21

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Etiology:

Table 4: Estimated marginal means in z-scores and standard errors for time for each etiology group and for every evaluation time, in Fluency

Time	etiology	*Mean*	*SE*
pre	MCD	-1.09	0.19
	tumor	-0.44	0.24
	dual pathology	-0.84	0.31
	vascular malformation	-1.83	0.74
	gliosis	0.14	0.44
	mesial temporal sclerosis	-0.40	0.47
	other	-0.55	1.04
6 mo	MCD	-1.04	0.21
	tumor	-0.05	0.24
	dual pathology	-0.32	0.31
	vascular malformation	-1.92	0.74
	gliosis	0.13	0.41
	mesial temporal sclerosis	0.16	0.55
12 mo	MCD	-0.75	0.23
	tumor	0.42	0.28
	dual pathology	-0.92	0.32
	vascular malformation	-0.94	0.74
	gliosis	0.17	0.44
	mesial temporal sclerosis	0.24	0.47
24 mo	MCD	-0.67	0.22
	tumor	0.19	0.27
	dual pathology	-0.89	0.34
	vascular malformation	-1.51	0.92
	gliosis	0.20	0.44
	mesial temporal sclerosis	-0.58	0.47
60 mo	MCD	-0.23	0.31
	tumor	0.68	0.44
	dual pathology	-1.14	0.54
	mesial temporal sclerosis	0.60	0.84
	other	0.50	1.04

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation, MCD = malformation of cortical development

Table 5 : Pairwise comparisons of Fluency scores in z-score differences for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each etiology group.

etiology	Time Pairwise Contrasts	Mean difference	SE	t	df	p
MCD	pre - 6 mo	-0.56	0.21	-0.27	140	.78
	pre - 12 mo	-0.35	0.23	-1.49	152	.14
	pre - 24 mo	-0.42	0.22	-1.92	148	.06
	pre - 60 mo	-0.87	0.34	-2.56	212	**.011**
	6 mo - 12 mo	-0.29	0.24	-1.20	153	.23
	12 mo - 24 mo	-0.08	0.25	-0.31	152	.76
	24 mo - 60 mo	-0.44	0.35	-1.27	209	.21
tumor	pre - 6 mo	-0.39	0.25	-1.59	144	.11
	pre - 12 mo	-0.86	0.28	-3.05	143	**.003**
	pre - 24 mo	-0.63	0.27	-2.33	145	**.021**
	pre - 60 mo	-1.12	0.46	-2.41	186	**.017**
	6 mo - 12 mo	-0.47	0.29	-1.60	151	.11
	12 mo - 24 mo	0.23	0.30	0.77	144	.44
	24 mo - 60 mo	-0.49	0.46	-1.08	176	.28
dual pathology	pre - 6 mo	-0.52	0.33	-1.59	146	.11
	pre - 12 mo	0.08	0.35	0.24	156	.81
	pre - 24 mo	0.05	0.36	0.14	155	.89
	pre - 60 mo	0.31	0.58	0.53	209	.60
	6 mo - 12 mo	0.60	0.34	1.78	146	.08
	12 mo - 24 mo	-0.03	0.36	-0.09	144	.93
	24 mo - 60 mo	0.25	0.61	0.42	211	.68
vascular malformation	pre - 6 mo	0.09	0.70	0.13	135	.90
	pre - 12 mo	-0.89	0.70	-1.27	135	.21
	pre - 24 mo	-0.32	0.89	-0.35	141	.72
	6 mo - 12 mo	-0.98	0.70	-1.40	135	.16
	12 mo - 24 mo	0.57	0.89	0.64	141	.52
gliosis	pre - 6 mo	0.01	0.43	0.03	137	.98
	pre - 12 mo	-0.02	0.47	-0.05	150	.96
	pre - 24 mo	-0.05	0.47	-0.11	150	.91
	6 mo - 12 mo	-0.04	0.44	-0.08	146	.94
	12 mo - 24 mo	-0.03	0.45	-0.07	139	.95
mesial temporal sclerosis	pre - 6 mo	-0.56	0.53	-1.06	140	.29
	pre - 12 mo	-0.64	0.44	-1.45	135	.15
	pre - 24 mo	0.18	0.44	0.41	135	.69
	pre - 60 mo	-1.00	0.83	-1.20	147	.23
	6 mo - 12 mo	-0.08	0.53	-0.15	140	.88
	12 mo - 24 mo	0.82	0.44	1.85	135	.07

	24 mo - 60 mo	-1.18	0.83	-1.42	147	.16
other	pre - 60 mo	-1.05	0.99	-1.06	135	.29

Note. Pre = presurgical evaluation, mo = months post-surgery, MCD = malformation of cortical development, bold print = significant result

Surgery type :

Table 6: Estimated marginal means in z-scores and standard errors for each surgery type group and for every evaluation time, in Fluency

Time	type of surgery	*Mean*	*SE*
pre	lesionectomy	-1.16	0.25
	intralobar tailored resection	-0.38	0.23
	multilobar tailored resection	-0.85	0.33
	AHE	0.29	0.63
	standard temporal resection +- AHE	-0.85	0.32
	temporal tailored resection + AHE	-1.24	0.44
6 mo	lesionectomy	-1.02	0.26
	intralobar tailored resection	-0.45	0.24
	multilobar tailored resection	-0.26	0.34
	AHE	0.53	0.71
	standard temporal resection +- AHE	-0.48	0.35
	temporal tailored resection + AHE	0.11	0.44
12 mo	lesionectomy	-0.52	0.31
	intralobar tailored resection	-0.06	0.26
	multilobar tailored resection	-0.44	0.35
	AHE	0.14	0.63
	standard temporal resection +- AHE	-0.36	0.34
	temporal tailored resection + AHE	-0.49	0.41
24 mo	lesionectomy	-0.52	0.27
	intralobar tailored resection	-0.32	0.25
	multilobar tailored resection	-0.34	0.38
	AHE	-0.12	0.63
	standard temporal resection +- AHE	-0.08	0.35
	temporal tailored resection + AHE	-1.41	0.44
60 mo	lesionectomy	0.14	0.47
	intralobar tailored resection	-0.10	0.38
	multilobar tailored resection	-0.57	0.49
	AHE	0.87	0.90
	standard temporal resection +- AHE	0.33	0.54

Note. AHE = amygdalohippocampectomy, mo = months post-surgery, pre = presurgical evaluation

Table 7: Overall F-Test of surgery type for every evaluation time in Fluency.

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	1.90	5	185	.10
6 mo	1.69	5	204	.14
12 mo	0.45	5	205	.82
24 mo	1.31	5	208	.26
60 mo	0.71	4	216	.59

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 8: Deviation contrasts in Fluency between the mean of the cohort and the different surgical groups for every evaluation time in z-scores

Time	type of surgery deviation contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	lesionectomy - Mean	-0.46	0.26	-1.80	151	.07
	intralobar tailored resection - Mean	0.32	0.25	1.30	148	.20
	multilobar tailored resection - Mean	-0.16	0.31	-0.50	161	.62
	AHE - Mean	0.99	0.54	1.84	130	.07
	standard temporal resection ± AHE - Mean	-0.15	0.31	-0.50	160	.62
	temporal tailored resection + AHE - Mean	-0.54	0.39	-1.37	182	.17
6 mo	lesionectomy - Mean	-0.76	0.27	-2.77	171	**.006**
	intralobar tailored resection - Mean	-0.19	0.26	-0.73	163	.47
	multilobar tailored resection - Mean	0.01	0.32	0.01	173	.99
	AHE - Mean	0.79	0.60	1.32	172	.19
	standard temporal resection ± AHE - Mean	-0.22	0.32	-0.69	165	.49
	temporal tailored resection + AHE - Mean	0.37	0.40	0.93	184	.36
12 mo	lesionectomy - Mean	-0.23	0.30	-0.77	199	.45
	intralobar tailored resection - Mean	0.23	0.27	0.84	178	.40
	multilobar tailored resection - Mean	-0.15	0.36	-0.46	182	.65
	AHE - Mean	0.43	0.54	0.80	131	.42
	standard temporal resection ± AHE - Mean	-0.07	0.32	-0.23	170	.82
	temporal tailored resection + AHE - Mean	-0.20	0.38	-0.55	169	.59
24 mo	lesionectomy - Mean	-0.06	0.28	-0.21	179	.83
	intralobar tailored resection - Mean	0.14	0.26	0.53	171	.60
	multilobar tailored resection - Mean	0.13	0.36	0.36	202	.72
	AHE - Mean	0.35	0.54	0.65	132	.52

	standard temporal resection ± AHE - Mean	0.39	0.33	1.17	180	.24
	temporal tailored resection + AHE - Mean	-0.94	0.40	-2.38	184	**.018**
60 mo	lesionectomy - Mean	0.01	0.45	0.02	214	.98
	intralobar tailored resection - Mean	-0.23	0.39	-0.59	215	.56
	multilobar tailored resection - Mean	-0.71	0.45	-1.54	210	.13
	AHE - Mean	0.74	0.74	0.99	215	.32
	standard temporal resection ± AHE - Mean	0.19	0.49	0.39	216	.70

Note. time= timing of perisurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy, bold print = significant result

Table 9: Pairwise comparisons of Fluency scores in z-scores for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgery type group

type of surgery	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
lesionectomy	pre - 6 mo	-0.15	0.25	-0.59	134	.56
	pre - 12 mo	-0.64	0.31	-2.09	144	**.038**
	pre - 24 mo	-0.64	0.28	-2.32	150	**.022**
	pre - 60 mo	-1.30	0.50	-2.60	212	**.010**
	6 mo - 12 mo	-0.50	0.32	-1.54	148	.13
	12 mo - 24 mo	0.01	0.33	0.01	147	.99
	24 mo - 60 mo	-0.67	0.50	-1.34	206	.18
intralobar tailored resection	pre - 6 mo	0.07	0.23	0.32	136	.75
	pre - 12 mo	-0.32	0.25	-1.26	138	.21
	pre - 24 mo	-0.05	0.24	-0.23	134	.82
	pre - 60 mo	-0.28	0.39	-0.72	190	.47
	6 mo - 12 mo	-0.39	0.26	-1.50	139	.14
	12 mo - 24 mo	0.26	0.27	0.97	139	.33
	24 mo - 60 mo	-0.23	0.41	-0.56	190	.58
multilobar tailored resection	pre - 6 mo	-0.60	0.32	-1.84	132	.07
	pre - 12 mo	-0.42	0.37	-1.13	158	.26
	pre - 24 mo	-0.52	0.39	-1.33	147	.19
	pre - 60 mo	-0.28	0.54	-0.52	213	.60
	6 mo - 12 mo	0.18	0.38	0.48	159	.63
	12 mo - 24 mo	-0.10	0.40	-0.26	142	.80
	24 mo - 60 mo	0.24	0.56	0.42	204	.68
AHE	pre - 6 mo	-0.24	0.66	-0.37	134	.71
	pre - 12 mo	0.15	0.57	0.26	131	.80
	pre - 24 mo	0.41	0.57	0.71	131	.480
	pre - 60 mo	-0.58	0.86	-0.67	139	.50
	6 mo - 12 mo	0.39	0.66	0.60	134	.55
	12 mo - 24 mo	0.26	0.57	0.45	131	.65
	24 mo - 60 mo	-0.99	0.86	-1.14	139	.25
standard temporal resection ± AHE	pre - 6 mo	-0.37	0.33	-1.13	144	.26
	pre - 12 mo	-0.49	0.34	-1.43	145	.16
	pre - 24 mo	-0.78	0.36	-2.16	147	**.032**
	pre - 60 mo	-1.18	0.56	-2.10	191	**.037**
	6 mo - 12 mo	-0.12	0.33	-0.36	136	.72
	12 mo - 24 mo	-0.29	0.35	-0.82	135	.42
	24 mo - 60 mo	-0.40	0.58	-0.69	192	.49
temporal tailored resection + AHE	pre - 6 mo	-1.34	0.50	-2.69	160	**.008**
	pre - 12 mo	-0.74	0.46	-1.61	148	.11
	pre - 24 mo	0.17	0.49	0.35	152	.73

6 mo - 12 mo	0.60	0.47	1.28	159	.20
12 mo - 24 mo	0.92	0.45	2.06	140	**.042**

Note. Pre = presurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy

Localization:

Table 10: Overall F-Test results of localization for every evaluation time in Fluency

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	1.50	4	197	.21
6 mo	3.58	4	204	**.008**
12 mo	0.82	5	219	.54
24 mo	0.65	5	205	.66
60 mo	0.63	3	219	.60

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 11: Estimated marginal means in z-scores and standard errors for every localization group for each evaluation time, in Fluency

Time	localization	*Mean*	*SE*
pre	frontal	-1.09	0.22
	temporal	-0.65	0.19
	parietal	-0.07	0.73
	occipital	0.24	0.63
	multilobar	-0.85	0.33
6 mo	frontal	-1.21	0.24
	temporal	-0.21	0.20
	parietal	0.19	0.73
	occipital	0.29	0.63
	multilobar	-0.26	0.34
12 mo	frontal	-0.69	0.28
	temporal	-0.10	0.20
	parietal	-0.43	0.92
	occipital	0.16	0.91
	multilobar	-0.44	0.35
	insular	-1.23	1.09
24 mo	frontal	-0.69	0.26
	temporal	-0.39	0.20
	parietal	0.06	0.70
	occipital	0.16	0.63
	multilobar	-0.33	0.39
	insular	-1.41	1.09
60 mo	frontal	-0.14	0.39
	temporal	0.10	0.37
	parietal	0.50	0.73
	multilobar	-0.57	0.49

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 12: Pairwise comparisons of Fluency scores in z-scores for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgical localization group.

Localization	Time Pairwise Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
	pre - 6 mo	0.13	0.23	0.56	139	.58
	pre - 12 mo	-0.40	0.27	-1.47	148	.14
	pre - 24 mo	-0.40	0.25	-1.59	143	.11
frontal	pre - 60 mo	-0.95	0.41	-2.29	213	**.023**
	6 mo - 12 mo	-0.52	0.28	-1.85	150	.07
	12 mo - 24 mo	-0.01	0.30	-0.01	150	.99
	24 mo - 60 mo	-0.55	0.43	-1.27	208	.21
	pre - 6 mo	-0.45	0.20	-2.20	148	**.029**
	pre - 12 mo	-0.55	0.20	-2.70	145	**.008**
	pre - 24 mo	-0.26	0.21	-1.27	149	.21
temporal	pre - 60 mo	-0.75	0.37	-2.01	175	**.046**
	6 mo - 12 mo	-0.10	0.21	-0.49	146	.62
	12 mo - 24 mo	0.28	0.21	1.36	143	.18
	24 mo - 60 mo	-0.48	0.38	-1.27	179	.21
	pre - 6 mo	-0.26	0.72	-0.36	136	.72
	pre - 12 mo	0.36	0.93	0.39	147	.70
	pre - 24 mo	-0.13	0.82	-0.15	184	.88
parietal	pre - 60 mo	-0.57	0.98	-0.58	217	.56
	6 mo - 12 mo	0.62	0.93	0.66	147	.51
	12 mo - 24 mo	-0.49	0.94	-0.52	159	.61
	24 mo - 60 mo	-0.44	0.83	-0.53	195	.60
	pre - 6 mo	-0.05	0.59	-0.08	136	.93
	pre - 12 mo	0.08	0.88	0.09	145	.93
occipital	pre - 24 mo	0.08	0.59	0.13	136	.90
	6 mo - 12 mo	0.13	0.88	0.14	145	.89
	12 mo - 24 mo	0.01	0.88	0.00	145	.99
insular	12 mo - 24 mo	0.18	1.01	0.18	136	.86
	pre - 6 mo	-0.60	0.33	-1.79	137	.08
	pre - 12 mo	-0.41	0.38	-1.09	164	.28
	pre - 24 mo	-0.52	0.40	-1.30	152	.20
multilobar	pre - 60 mo	-0.28	0.54	-0.51	217	.61
	6 mo - 12 mo	0.19	0.38	0.49	165	.63
	12 mo - 24 mo	-0.11	0.41	-0.27	148	.79
	24 mo - 60 mo	0.24	0.57	0.42	209	.68

Note : pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Seizure Outcome:

Table 13: Estimated marginal means and standard errors for Fluency in z-scores for every evaluation time and for every seizure outcome group (in Engel categories)

Time	Seizure outcome	*Mean*	*SE*
pre	0	-0.77	0.13
6 mo	1a	-0.62	0.15
	> 1a	-0.22	0.24
12 mo	1a	-0.44	0.16
	> 1a	-0.08	0.24
24 mo	1a	-0.53	0.17
	> 1a	-0.36	0.21
60 mo	1a	-0.24	0.30
	> 1a	0.13	0.33

Note. Pre = presurgical evaluation, mo = months post-surgery

Antiseizure drug (ASM) load:

Table 14: Estimated marginal means and standard errors for Fluency in z-scores for every evaluation time and for every antiseizure drug load group

Time	ASM	*Mean*	*SE*
pre	1	-0.69	0.22
	> 1	-0.79	0.14
6 mo	1	-0.50	0.18
	> 1	-0.50	0.19
12 mo	1	-0.33	0.18
	> 1	-0.38	0.22
	0	-0.06	0.48
24 mo	1	-0.48	0.19
	> 1	-0.61	0.29
	0	-0.30	0.23
60 mo	1	0.13	0.33
	> 1	-0.44	0.40
	0	0.05	0.44

Note. Pre = presurgical evaluation, mo = months post-surgery, ASM = number of antiseizure medications

Table 15: Pairwise comparisons of Fluency in z-scores between the antiseizure drug load groups (ASM) for each evaluation time.

Time	ASM Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
pre	1 - > 1	0.09	0.24	0.40	183	.69
6 mo	1 - > 1	-0.01	0.23	-0.03	189	.98
	1 - > 1	0.06	0.27	0.21	194	.84
12 mo	0 - 1	0.27	0.50	0.54	168	.59
	0 - > 1	0.33	0.52	0.63	174	.53
	1 - > 1	0.13	0.33	0.41	194	.69
24 mo	0 - 1	0.18	0.27	0.66	172	.51
	0 - > 1	0.31	0.35	0.87	196	.38
	1 - > 1	0.57	0.52	1.09	232	.28
60 mo	0 - 1	-0.08	0.55	-0.14	210	.89
	0 - > 1	0.49	0.60	0.82	227	.42

Note. Pre = presurgical evaluation, mo = months post-surgery, ASM = antiseizure medication

8.7. Appendix 7

Working Memory Analyses

Side of surgery:

Table 1 : Estimated marginal means in scaled score points and standard errors for each evaluation time and for every side of surgery, in Working Memory

Time	hemisphere	*Mean*	*SE*
pre	right	8.05	0.36
	left	9.03	0.40
6 mo	right	8.04	0.43
	left	9.03	0.44
12 mo	right	8.25	0.40
	left	9.83	0.41
24 mo	right	8.67	0.42
	left	9.93	0.44
60 mo	right	8.46	0.87
	left	10.18	0.69

Note. Pre = persurgical evaluation, mo = months post-surgery

Etiology :

Table 2 : Estimated marginal means in scaled score points and standard errors for time for each etiology group and for every evaluation time, in Working Memory

Time	etiology	*Mean*	*SE*
pre	MCD	7.66	0.42
	tumor	8.99	0.51
	dual pathology	8.54	0.63
	vascular malformation	9.00	1.93
	gliosis	10.14	1.07
	mesial temporal sclerosis	10.00	1.22
	other	11.00	2.73
6 mo	MCD	7.52	0.46
	tumor	9.32	0.61
	dual pathology	8.62	0.71
	vascular malformation	8.50	1.93
	gliosis	9.68	1.33
	mesial temporal sclerosis	10.50	1.58
12 mo	MCD	7.96	0.45
	tumor	10.25	0.55
	dual pathology	8.83	0.68
	vascular malformation	10.00	1.93
	gliosis	9.59	1.08
	mesial temporal sclerosis	10.20	1.22
24 mo	MCD	8.69	0.50
	tumor	9.69	0.58
	dual pathology	8.76	0.67
	vascular malformation	8.04	2.33
	gliosis	9.75	1.33
	mesial temporal sclerosis	12.00	1.22
60 mo	MCD	8.57	0.84
	tumor	10.88	1.14
	dual pathology	8.45	1.14
	mesial temporal sclerosis	11.77	2.05
	other	11.00	2.73

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation, MCD = malformation of cortical development

Table 3 : Deviation contrasts in Working Memory between the mean of the cohort and the different etiology groups for every evaluation time in scaled score points

Time	etiology deviation contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	MCD - Mean	-1.67	0.65	-2.57	160	**.011**
	tumor - Mean	-0.35	0.70	-0.50	163	.62
	dual pathology - Mean	-0.79	0.76	-1.03	164	.30
	vascular malformation - Mean	-0.33	1.72	-0.19	157	.85
	gliosis - Mean	0.81	1.06	0.76	171	.45
	mesial temporal sclerosis - Mean	0.67	1.17	0.57	157	.57
	other - Mean	1.67	2.38	0.70	157	.48
6 mo	MCD - Mean	-1.50	0.63	-2.39	214	**.018**
	tumor - Mean	0.30	0.71	0.42	230	.68
	dual pathology - Mean	-0.41	0.76	-0.54	219	.59
	vascular malformation - Mean	-0.52	1.66	-0.32	162	.75
	gliosis - Mean	0.66	1.20	0.55	254	.58
	mesial temporal sclerosis - Mean	1.48	1.39	1.07	263	.29
12 mo	MCD - Mean	-1.51	0.58	-2.60	176	**.010**
	tumor - Mean	0.78	0.64	1.22	183	.23
	dual pathology - Mean	-0.64	0.71	-0.90	186	.37
	vascular malformation - Mean	0.53	1.64	0.32	157	.75
	gliosis - Mean	0.12	0.99	0.12	173	.90
	mesial temporal sclerosis - Mean	0.73	1.10	0.66	158	.51
24 mo	MCD - Mean	-0.80	0.66	-1.20	236	.23
	tumor - Mean	0.21	0.70	0.29	227	.77
	dual pathology - Mean	-0.73	0.76	-0.96	216	.34
	vascular malformation - Mean	-1.45	1.97	-0.74	244	.46
	gliosis - Mean	0.26	1.21	0.22	256	.83
	mesial temporal sclerosis - Mean	2.51	1.13	2.23	171	**.027**
60 mo	MCD - Mean	-1.56	1.01	-1.55	285	.12
	tumor - Mean	0.74	1.18	0.63	292	.53
	dual pathology - Mean	-1.68	1.17	-1.43	291	.15
	mesial temporal sclerosis - Mean	1.64	1.77	0.93	292	.35
	other - Mean	0.87	2.26	0.38	167	.70

Table 4 : Pairwise comparisons of Working memory scores in scaled score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgery type group

etiology	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p*
	pre - 6 mo	0.14	.41	0.34	202	.74
	pre - 12 mo	-0.30	.39	-0.77	201	.44
	pre - 24 mo	-1.03	.45	-2.29	202	**.023**
MCD	pre - 60 mo	-0.91	.82	-1.12	227	.27
	6 mo - 12 mo	-0.44	.43	-1.03	196	.30
	12 mo - 24 mo	-0.73	.46	-1.58	197	.12
	24 mo - 60 mo	0.12	.86	0.14	223	.89
	pre - 6 mo	-0.34	.56	-0.60	205	.55
	pre - 12 mo	-1.26	.49	-2.58	200	**.015**
	pre - 24 mo	-0.71	.53	-1.35	206	.18
tumor	pre - 60 mo	-1.89	1.12	-1.69	211	.09
	6 mo - 12 mo	-0.93	.59	-1.59	202	.11
	12 mo - 24 mo	0.56	.55	1.01	202	.31
	24 mo - 60 mo	-1.18	1.14	-1.04	209	.30
	pre - 6 mo	-0.07	.63	-0.12	198	.91
	pre - 12 mo	-0.29	.60	-0.48	200	.63
	pre - 24 mo	-0.22	.61	-0.35	206	.73
dual pathology	pre - 60 mo	0.09	1.09	0.08	200	.93
	6 mo - 12 mo	-0.22	.68	-0.32	202	.75
	12 mo - 24 mo	0.07	.63	0.12	198	.91
	24 mo - 60 mo	0.32	1.11	0.28	200	.78
	pre - 6 mo	0.50	1.62	0.31	191	.76
	pre - 12 mo	-1.00	1.62	-0.62	191	.54
vascular malformation	pre - 24 mo	0.96	2.08	0.46	197	.64
	6 mo - 12 mo	-1.50	1.62	-0.93	191	.36
	12 mo - 24 mo	1.96	2.08	0.95	197	.35
	pre - 6 mo	0.46	1.28	0.36	214	.72
	pre - 12 mo	0.55	.98	0.56	204	.58
gliosis	pre - 24 mo	0.39	1.28	0.31	214	.76
	6 mo - 12 mo	0.09	1.22	0.08	201	.94
	12 mo - 24 mo	-0.16	1.22	-0.13	201	.90
	pre - 6 mo	-0.50	1.44	-0.35	198	.73
	pre - 12 mo	-0.20	1.03	-0.20	191	.85
	pre - 24 mo	-2.00	1.03	-1.95	191	.053
mesial temporal sclerosis	pre - 60 mo	-1.77	1.94	-0.92	202	.36
	6 mo - 12 mo	0.30	1.44	0.21	198	.83
	12 mo - 24 mo	-1.80	1.03	-1.76	191	.08
	24 mo - 60 mo	0.23	1.94	0.12	202	.91

other	pre - 60 mo	-0.01	2.30	-0.01	191	.99

Note. Pre = presurgical evaluation, mo = months post-surgery, MCD = malformation cortical development

Surgery type :

Table 5 : Overall F-Test of surgery type for every evaluation time in Working Memory

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	1.20	5	198	.31
6 mo	1.72	5	265	.13
12 mo	1.07	5	228	.38
24 mo	1.82	5	255	.11
60 mo	1.40	4	293	.23

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 6 : Overall F-Test of time for every type of surgery in Working Memory

type of surgery	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
lesionectomy	1.24	4	203	.30
intralobar tailored resection	1.81	4	210	.13
multilobar tailored resection	0.56	4	201	.70
AHE	0.88	4	194	.48
standard temporal resection +- AHE	0.28	4	200	.89
temporal tailored resection + AHE	0.15	3	203	.93

Note. Pre = presurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy

Table 7 : Estimated marginal means and standard errors in scaled score points for each surgery type group and for every evaluation time in Working Memory

Time	type of surgery	*Mean*	*SE*
pre	lesionectomy	8.64	0.54
	intralobar tailored resection	8.07	0.48
	multilobar tailored resection	8.32	0.63
	AHE	11.00	1.59
	standard temporal resection ± AHE	8.16	0.72
	temporal tailored resection + AHE	9.94	0.95
6 mo	lesionectomy	8.95	0.61
	intralobar tailored resection	7.50	0.56
	multilobar tailored resection	8.26	0.82
	AHE	11.58	1.76
	standard temporal resection ± AHE	8.58	0.75
	temporal tailored resection + AHE	9.82	1.04
12 mo	lesionectomy	9.37	0.58
	intralobar tailored resection	8.64	0.50
	multilobar tailored resection	8.83	0.69
	AHE	11.67	1.59
	standard temporal resection ± AHE	8.35	0.77
	temporal tailored resection + AHE	9.92	1.04
24 mo	lesionectomy	9.38	0.59
	intralobar tailored resection	8.72	0.59
	multilobar tailored resection	9.01	0.74
	AHE	13.33	1.59
	standard temporal resection +- AHE	8.79	0.77
	temporal tailored resection + AHE	10.54	1.17
60 mo	lesionectomy	10.47	1.02
	intralobar tailored resection	9.05	1.05
	multilobar tailored resection	7.63	1.39
	AHE	12.85	2.20
	standard temporal resection ±AHE	8.73	1.21

Note. Pre = presurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy

Table 8 : Deviation contrasts in Working Memory between the mean of the cohort and the different surgical groups for every evaluation time in scaled score points

Time	type of surgery Deviation Contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	lesionectomy - Mean	-0.38	0.57	-0.67	168	.51
	intralobar tailored resection - Mean	-0.95	0.54	-1.78	166	.08
	multilobar tailored resection - Mean	-0.70	0.63	-1.11	159	.27
	AHE - Mean	1.98	1.35	1.47	158	.14
	standard temporal resection +- AHE - Mean	-0.86	0.70	-1.24	165	.22
	temporal tailored resection + AHE - Mean	0.92	0.86	1.07	170	.29
6 mo	lesionectomy - Mean	-0.16	0.65	-0.25	224	.80
	intralobar tailored resection - Mean	-1.62	0.61	-2.65	227	**.009**
	multilobar tailored resection - Mean	-0.85	0.78	-1.09	253	.28
	AHE - Mean	2.46	1.50	1.65	209	.10
	standard temporal resection +- AHE - Mean	-0.54	0.74	-0.72	195	.47
	temporal tailored resection + AHE - Mean	0.71	0.94	0.75	210	.45
12 mo	lesionectomy - Mean	-0.09	0.61	-0.15	196	.88
	intralobar tailored resection - Mean	-0.82	0.56	-1.48	183	.14
	multilobar tailored resection - Mean	-0.63	0.68	-0.93	191	.35
	AHE - Mean	2.21	1.35	1.63	159	.11
	standard temporal resection +- AHE - Mean	-1.12	0.74	-1.52	192	.13
	temporal tailored resection + AHE - Mean	0.46	0.93	0.50	204	.62
24 mo	lesionectomy - Mean	-0.58	0.63	-0.93	209	.36
	intralobar tailored resection - Mean	-1.24	0.62	-1.99	235	**.048**
	multilobar tailored resection - Mean	-0.95	0.73	-1.31	220	.19
	AHE - Mean	3.37	1.36	2.48	161	**.014**
	standard temporal resection +- AHE - Mean	-1.17	075	-1.57	198	.12
	temporal tailored resection + AHE - Mean	0.58	1.04	0.55	251	.58
60 mo	lesionectomy - Mean	0.72	1.02	0.71	287	.48
	intralobar tailored resection - Mean	-0.70	1.05	-0.67	289	.50
	multilobar tailored resection - Mean	-2.11	1.25	-1.69	276	.09
	AHE - Mean	3.10	1.82	1.70	287	.09
	standard temporal resection +- AHE - Mean	-1.02	1.14	-0.89	292	.37

Note. Pre = presurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy, bold print = significant result

Table 9 : Pairwise comparisons of Working memory in scaled score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgery type group

type of surgery	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p*
lesionectomy	pre - 6 mo	-0.32	0.55	-0.57	202	.57
	pre - 12 mo	-0.73	0.52	-1.41	200	.16
	pre - 24 mo	-0.75	0.55	-1.37	211	.17
	pre - 60 mo	-1.83	0.99	-1.85	208	.07
	6 mo - 12 mo	-0.41	0.58	-0.71	197	.48
	12 mo - 24 mo	-0.02	0.57	-0.03	202	.97
	24 mo - 60 mo	-1.09	1.01	-1.08	206	.28
intralobar tailored resection	pre - 6 mo	0.57	0.51	1.12	203	.26
	pre - 12 mo	-0.57	0.44	-1.30	198	.20
	pre - 24 mo	-0.66	0.53	-1.24	201	.22
	pre - 60 mo	-0.99	1.04	-0.95	241	.34
	6 mo - 12 mo	-1.14	0.51	-2.24	197	**.026**
	12 mo - 24 mo	-0.09	0.55	-0.16	204	.88
	24 mo - 60 mo	-0.33	1.10	-0.30	240	.77
multilobar tailored resection	pre - 6 mo	0.05	0.74	0.07	205	.94
	pre - 12 mo	-0.51	0.60	-0.85	201	.40
	pre - 24 mo	-0.70	0.66	-1.06	203	.29
	pre - 60 mo	0.68	1.35	0.51	203	.61
	6 mo - 12 mo	-0.56	0.79	-0.71	205	.48
	12 mo - 24 mo	-0.19	0.68	-0.28	194	.78
	24 mo - 60 mo	1.38	1.37	1.01	199	.32
AHE	pre - 6 mo	-0.58	1.54	-0.38	194	.71
	pre - 12 mo	-0.67	1.34	-0.50	190	.62
	pre - 24 mo	-2.33	1.34	-1.74	190	.08
	pre - 60 mo	-1.85	2.03	-0.91	199	.36
	6 mo - 12 mo	-0.09	1.54	-0.06	194	.95
	12 mo - 24 mo	-1.67	1.34	-1.24	190	.22
	24 mo - 60 mo	0.49	2.03	0.24	199	.81
standard temporal resection ± AHE	pre - 6 mo	-0.42	0.66	-0.65	192	.52
	pre - 12 mo	-0.18	0.69	-0.27	199	.79
	pre - 24 mo	-0.64	0.69	-0.92	199	.36
	pre - 60 mo	-0.58	1.15	-0.50	207	.62
	6 mo - 12 mo	0.24	0.72	0.34	199	.74
	12 mo - 24 mo	-0.46	0.70	-0.65	190	.52
	24 mo - 60 mo	0.06	1.20	0.05	211	.96
temporal tailored resection + AHE	pre - 6 mo	0.12	0.95	0.12	208	.90
	pre - 12 mo	0.01	0.95	0.01	210	.99
	pre - 24 mo	-0.60	1.11	-0.54	212	.59

6 mo - 12 mo	-0.10	0.98	-0.11	195	.92
12 mo - 24 mo	-0.62	1.09	-0.56	194	.57

Note. Pre = presurgical evaluation, mo = months post-surgery, AHE = amygdalohippocampectomy, bold print = significant result

Localization :

Table 10 : Overall test results of localization groups for every evaluation time in Working Memory

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	1.15	5	192	.34
6 mo	2.17	4	271	.07
12 mo	1.00	5	211	.43
24 mo	1.69	4	294	.15
60 mo	1.06	3	296	.37

Table 11 : Estimated marginal means and standard errors in scaled score points for every localization group for each evaluation time, in Working Memory

Time	localization	*Mean*	*SE*
pre	frontal	7.73	0.49
	temporal	9.09	0.42
	parietal	9.42	1.09
	occipital	7.33	1.60
	insular	8.00	2.78
	multilobar	8.32	0.64
6 mo	frontal	7.36	0.53
	temporal	9.30	0.49
	parietal	9.76	1.15
	occipital	8.50	1.78
	multilobar	8.25	0.82
12 mo	frontal	8.48	0.51
	temporal	9.23	0.46
	parietal	10.52	1.15
	occipital	7.67	1.60
	insular	12.00	2.78
	multilobar	8.82	0.69
24 mo	frontal	8.62	0.57
	temporal	9.75	0.46
	parietal	11.31	1.52
	occipital	6.50	1.78
	multilobar	9.01	0.74
60 mo	frontal	9.34	0.94

temporal	9.75	0.98
parietal	10.96	1.34
multilobar	7.62	1.37

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 12 : Deviation contrasts in Working Memory between the mean of the cohort and the different localization groups for every evaluation time in scaled score points

Time	Localization Deviation Contrasts	Contrast Estimate	*SE*	*t*	*df*	*p*
pre	frontal - Mean	-0.58	0.71	-0.82	161	.41
	temporal - Mean	0.77	0.68	1.14	158	.26
	parietal - Mean	1.10	1.07	1.04	168	.30
	occipital - Mean	-0.98	1.43	-0.68	155	.50
	insular - Mean	-0.31	2.34	-0.13	155	.89
	multilobar - Mean	0.002	0.78	0.01	156	.99
6 mo	frontal - Mean	-1.27	0.63	-2.03	208	**.044**
	temporal - Mean	0.66	0.61	1.10	218	.28
	parietal - Mean	1.13	1.01	1.12	199	.27
	occipital - Mean	-0.13	1.46	-0.09	206	.93
	multilobar - Mean	-0.39	0.79	-0.49	245	.63
12 mo	frontal - Mean	-0.97	0.72	-1.34	168	.18
	temporal - Mean	-0.23	0.70	-0.32	172	.75
	parietal - Mean	1.06	1.11	0.96	186	.34
	occipital - Mean	-1.79	1.44	-1.24	156	.22
	insular - Mean	2.55	2.34	1.09	155	.28
	multilobar - Mean	-0.63	0.82	-0.77	176	.44
24 mo	frontal - Mean	-0.42	0.67	-0.62	240	.54
	temporal - Mean	0.71	0.63	1.14	232	.26
	parietal - Mean	2.27	1.28	1.77	287	.08
	occipital - Mean	-2.54	1.47	-1.73	210	.09
	multilobar - Mean	-0.03	0.77	-0.04	233	.97
60 mo	frontal - Mean	-0.08	0.88	-0.10	294	.93
	temporal - Mean	0.33	0.91	0.37	283	.71
	parietal - Mean	1.54	1.11	1.39	279	.17
	multilobar - Mean	-1.80	1.13	-1.59	280	.11

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Table 13 : Pairwise comparisons of Working memory scores in scaled score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgical localization subgroup.

localization	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
	pre - 6 mo	0.37	0.46	0.80	201	.42
	pre - 12 mo	-0.75	0.44	-1.73	198	.09
	pre - 24 mo	-0.89	0.51	-1.75	206	.08
frontal	pre - 60 mo	-1.61	0.92	-1.74	236	.08
	6 mo - 12 mo	-1.13	0.47	-2.40	197	**.017**
	12 mo - 24 mo	-0.14	0.52	-0.27	205	.79
	24 mo - 60 mo	-0.71	0.96	-0.74	234	.46
	pre - 6 mo	-0.21	0.43	-0.49	204	.63
	pre - 12 mo	-0.14	0.40	-0.35	204	.73
	pre - 24 mo	-0.67	0.41	-1.63	207	.10
temporal	pre - 60 mo	-0.66	0.95	-0.70	212	.49
	6 mo - 12 mo	0.07	0.46	0.15	201	.88
	12 mo - 24 mo	-0.53	0.42	-1.24	198	.22
	24 mo - 60 mo	.002	0.97	0.003	213	.99
	pre - 6 mo	-0.34	1.04	-0.33	209	.74
	pre - 12 mo	-1.10	1.05	-1.05	211	.29
	pre - 24 mo	-1.90	1.41	-1.34	205	.18
parietal	pre - 60 mo	-1.54	1.21	-1.27	206	.21
	6 mo - 12 mo	-0.76	1.06	-0.72	200	.48
	12 mo - 24 mo	-0.80	1.42	-0.56	200	.58
	24 mo - 60 mo	0.35	1.51	0.23	196	.82
	pre - 6 mo	-1.17	1.53	-0.76	200	.45
	pre - 12 mo	-0.33	1.31	-0.25	193	.80
occipital	pre - 24 mo	0.83	1.53	0.55	200	.59
	6 mo - 12 mo	0.83	1.56	0.55	200	.59
	12 mo - 24 mo	1.17	1.53	0.76	200	.45
insular	pre - 12 mo	-4.00	2.28	-1.76	193	.08
	pre - 6 mo	0.07	0.73	0.09	207	.93
	pre - 12 mo	-0.50	0.59	-0.85	203	.40
	pre - 24 mo	-0.69	0.65	-1.07	205	.28
multilobar	pre - 60 mo	0.70	1.32	0.53	205	.60
	6 mo - 12 mo	-0.57	0.77	-0.74	208	.46
	12 mo - 24 mo	-0.19	0.66	-0.29	197	.78
	24 mo - 60 mo	1.39	1.34	1.04	202	.30

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Seizure outcome:

Table 14 : Estimated marginal means and standard errors for Working Memory in scaled score points for every evaluation time and for every seizure outcome group (in Engel categories)

Time	Engel	*Mean*	*SE*
pre	/	8.50	0.28
6 mo	1a	8.50	0.34
	> 1a	8.35	0.54
12 mo	1a	9.08	0.33
	> 1a	8.75	0.45
24 mo	1a	9.21	0.38
	> 1a	9.33	0.43
60 mo	1a	9.293	.833
	> 1a	9.501	.780

Note. Pre = presurgical evaluation, mo = months post-surgery, Engel = seizure outcome expressed in Engel categories.

AED load:

Table 15: Estimated marginal means and standard errors for Working Memory in scaled score points for every evaluation time and for every antiseizure drug load subgroup

Time	AED	*Mean*	*SE*
pre	0	12.02	1.42
	1	9.02	0.42
	> 1	8.20	0.30
6 mo	1	8.72	0.38
	> 1	8.11	0.41
12 mo	0	10.89	0.86
	1	9.09	0.35
	> 1	8.63	0.40
24 mo	0	9.90	0.52
	1	9.20	0.34
	> 1	8.88	0.51
60 mo	0	9.00	1.50
	1	9.78	0.78
	> 1	8.71	0.94

Note. Pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

8.8. Appendix 8

Analyses of Executive Function Inhibition

Side of surgery:

Table 1 : Estimated marginal means in standard scores and standard errors for each evaluation time and for every side of surgery, in Inhibition

Time	Side of surgery	Mean	*SE*
pre	right	97.67	2.40
	left	104.15	2.65
6 mo	right	101.51	2.55
	left	105.66	2.75
12 mo	right	101.58	3.07
	left	105.06	2.64
24 mo	right	102.17	3.02
	left	107.42	2.60
60 mo	right	102.68	3.07
	left	107.31	3.41

Note. Pre = persurgical evaluation, mo = months post-surgery

Etiology:

Table 2 : Estimated marginal means in standard scores and standard errors for time for each etiology group and for every evaluation time, in Inhibition

Time	etiology	Mean	*SE*
pre	MCD	99.33	2.70
	tumor	105.74	3.89
	dual pathology	99.93	3.84
	vascular malformation	107.00	11.53
	gliosis	104.00	11.53
	mesial temporal sclerosis	102.18	6.13
	other	83.00	11.53
6 mo	MCD	97.09	2.86
	tumor	108.05	4.44
	dual pathology	107.89	3.63
	vascular malformation	114.00	11.53
	gliosis	108.00	11.53
	mesial temporal sclerosis	104.23	6.81
12 mo	MCD	95.73	3.26
	tumor	110.32	4.00
	dual pathology	105.46	3.83
	vascular malformation	114.00	11.53
	mesial temporal sclerosis	105.55	6.74
24 mo	MCD	101.82	3.03
	tumor	109.46	3.86
	dual pathology	103.40	4.52
	vascular malformation	118.00	11.53
	gliosis	99.00	11.53
	mesial temporal sclerosis	109.19	6.19
60 mo	MCD	101.02	3.02
	tumor	111.96	5.02
	dual pathology	101.23	7.17
	mesial temporal sclerosis	102.12	8.20
	other	104.00	11.53

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation, MCD = malformation of cortical development

Table 3 : Deviation contrasts in Inhibition between the mean of the cohort and the different etiology groups for every evaluation time in standard scores

Time	etiology Deviation Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	MCD - Mean	-0.84	3.86	-0.22	64	.83
	tumor - Mean	5.57	4.52	1.23	65	.22
	dual pathology - Mean	-0.23	4.49	-0.05	65	.96
	vascular malformation - Mean	6.83	10.23	0.67	55	.51
	gliosis - Mean	3.83	10.23	0.38	55	.71
	mesial temporal sclerosis - Mean	2.01	6.04	0.33	64	.74
	other - Mean	-17.17	10.23	-1.68	55	.10
6 mo	MCD - Mean	-9.45	3.91	-2.42	70	**.018**
	tumor - Mean	1.50	4.79	0.31	81	.75
	dual pathology - Mean	1.35	4.31	0.31	62	.76
	vascular malformation - Mean	7.46	9.92	0.75	55	.46
	gliosis - Mean	1.46	9.92	0.15	55	.88
	mesial temporal sclerosis - Mean	-2.32	6.38	-0.36	78	.72
12 mo	MCD - Mean	-10.49	3.89	-2.70	82	**.009**
	tumor - Mean	4.11	4.28	0.96	73	.34
	dual pathology - Mean	-0.75	4.19	-0.18	69	.86
	vascular malformation - Mean	7.79	9.41	0.83	56	.41
	mesial temporal sclerosis - Mean	-0.66	6.00	-0.11	78	.91
24 mo	MCD - Mean	-4.99	3.98	-1.26	73	.21
	tumor - Mean	2.65	4.43	0.60	66	.55
	dual pathology - Mean	-3.42	4.83	-0.71	81	.48
	vascular malformation - Mean	11.19	9.92	1.13	55	.26
	gliosis - Mean	-7.81	9.92	-0.79	55	.43
	mesial temporal sclerosis - Mean	2.38	5.93	0.40	65	.69
60 mo	MCD - Mean	-3.05	4.11	-0.74	88	.46
	tumor - Mean	7.90	5.16	1.53	94	.13
	dual pathology - Mean	-2.84	6.50	-0.44	91	.66
	mesial temporal sclerosis - Mean	-1.94	7.19	-0.27	97	.79

other - Mean	-0.07	9.55	-0.01	59	.99

Note. pre = presurgical evaluation, mo = months post-surgery, MCD = malformation of cortical development, bold print = significant result

Table 4 : Pairwise comparisons of Inhibition in standard score differences for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each etiology group.

etiology	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p*
MCD	pre - 6 mo	2.24	2.50	0.89	55	.38
	pre - 12 mo	3.60	3.06	1.18	57	.25
	pre - 24 mo	-2.49	2.76	-0.91	56	.37
	pre - 60 mo	-1.69	3.15	-0.54	71	.59
	6 mo - 12 mo	1.36	3.23	0.42	57	.68
	12 mo -24 mo	-6.10	3.10	-1.96	53	.055
	24 mo - 60 mo	0.80	3.33	0.24	66	.81
tumor	pre - 6 mo	-2.10	3.79	-0.61	52	.55
	pre - 12 mo	-4.58	3.38	-1.36	53	.18
	pre - 24 mo	-3.73	3.52	-1.06	59	.30
	pre - 60 mo	-6.23	4.96	-1.26	65	.21
	6 mo - 12 mo	-2.28	3.99	-0.57	53	.57
	12 mo - 24 mo	0.86	3.44	0.25	55	.80
	24 mo - 60 mo	-2.50	4.76	-0.53	63	.60
dual pathology	pre - 6 mo	-7.95	3.03	-2.63	52	**.011**
	pre - 12 mo	-5.53	3.32	-1.66	53	.10
	pre - 24 mo	-3.46	4.41	-0.79	61	.44
	pre - 60 mo	-1.30	7.09	-0.18	54	.86
	6 mo - 12 mo	2.43	3.03	0.80	52	.43
	12 mo - 24 mo	2.06	4.24	0.49	60	.63
	24 mo - 60 mo	2.16	7.01	0.31	53	.76
vascular malformation	pre - 6 mo	-7.00	8.06	-0.87	50	.39
	pre - 12 mo	-7.00	8.06	-0.87	50	.39
	pre - 24 mo	-11.00	8.06	-0.01	50	.18
	6 mo - 12 mo	-0.01	8.06	-0.01	50	.99
	12 mo - 24 mo	-4.00	8.06	-0.50	50	.62
gliosis	pre - 6 mo	-4.00	8.06	-0.50	50	.62
	pre - 24 mo	5.00	8.06	0.62	50	.54
mesial temporal sclerosis	pre - 6 mo	-2.05	6.18	-0.33	60	.74
	pre - 12 mo	-3.38	5.57	-0.61	54	.55
	pre - 24 mo	-7.02	5.27	-1.33	58	.19
	pre - 60 mo	0.05	7.21	0.01	53	.99
	6 mo - 12 mo	-1.33	6.36	-0.21	54	.84
	12 mo - 24 mo	-3.64	5.45	-0.67	52	.51
	24 mo - 60 mo	7.07	7.19	0.98	53	.33
other	pre - 60 mo	-21.00	8.06	-2.61	50	**.012**

Note. Pre = presurgical evaluation, mo = months post-surgery, MCD = malformation of cortical development, bold print = significant result

Localization:

Table 5 : Estimated marginal means in standard scores and standard errors for every localization group for each evaluation time, in Inhibition

Time	localization	Mean	*SE*
pre	frontal	99.94	3.44
	temporal	102.37	2.26
	parietal	103.73	8.58
	multilobar	96.91	4.70
6 mo	frontal	100.99	3.66
	temporal	106.91	2.40
	multilobar	95.65	4.64
	insular	89.00	10.97
12 mo	frontal	103.29	4.01
	temporal	105.13	2.53
	parietal	116.02	7.05
	multilobar	90.32	5.03
24 mo	frontal	106.26	3.73
	temporal	105.53	2.44
	parietal	114.67	6.33
	multilobar	97.99	7.33
60 mo	frontal	106.43	5.60
	temporal	107.08	3.49
	parietal	126.31	8.58
	multilobar	93.68	4.09
	insular	102.00	10.97

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 6 : Pairwise comparisons of Inhibition in standard scores for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgical localization group.

localization	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
	pre - 6 mo	-1.06	3.15	-0.33	64	.74
	pre - 12 mo	-3.36	3.43	-0.98	62	.33
	pre - 24 mo	-6.33	3.33	-1.90	65	.062
frontal	pre - 60 mo	-6.50	6.15	-1.06	105	.29
	6 mo - 12 mo	-2.30	3.67	-0.63	63	.53
	12 mo - 24 mo	-2.97	3.88	-0.77	65	.46
	24 mo - 60 mo	-.17	5.92	-0.03	104	.98
	pre - 6 mo	-4.55	2.08	-2.19	63	**.033**
	pre - 12 mo	-2.77	2.29	-1.21	64	.23
	pre - 24 mo	-3.17	2.25	-1.41	68	.16
temporal	pre - 60 mo	-4.71	3.28	-1.44	64	.16
	6 mo - 12 mo	1.78	2.33	0.77	62	.45
	12 mo - 24 mo	-.40	2.38	-0.17	63	.87
	24 mo - 60 mo	-1.55	3.42	-0.45	65	.65
	pre - 12 mo	-12.29	7.58	-1.62	62	.11
	pre - 24 mo	-10.94	7.48	-1.46	65	.15
parietal	pre - 60 mo	-22.58	9.77	-2.31	66	**.024**
	12 mo - 24 mo	1.36	5.66	0.24	64	.81
	24 mo - 60 mo	-11.65	7.48	-1.56	65	.12
insular	6 mo - 60 mo	-13.00	8.20	-1.59	59	.12
	pre - 6 mo	1.26	4.31	0.29	61	.77
	pre - 12 mo	6.59	5.28	1.25	70	.22
	pre - 24 mo	-1.08	7.64	-0.14	66	.89
multilobar	pre - 60 mo	3.23	4.90	0.66	83	.51
	6 mo - 12 mo	5.34	5.30	1.01	70	.32
	12 mo - 24 mo	-7.68	7.29	-1.05	62	.30
	24 mo - 60 mo	4.31	7.09	0.61	65	.55

Note. pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Type of surgery:

Table 7 : Estimated marginal means and standard errors in Inhibition in standard scores for every type of surgery group for all evaluation times

Time	type of surgery	*Mean*	*SE*
pre	lesionectomy	102.08	3.87
	intralobar tailored resection	99.52	4.13
	multilobar tailored resection	96.60	4.77
	AHE	106.50	8.14
	standard temporal resection ± AHE	102.33	3.70
	temporal tailored resection + AHE	100.25	4.04
6 mo	lesionectomy	104.19	3.83
	intralobar tailored resection	100.32	4.40
	multilobar tailored resection	95.28	4.71
	AHE	109.84	9.25
	standard temporal resection ±AHE	108.76	3.79
	temporal tailored resection + AHE	104.44	4.42
12 mo	lesionectomy	103.40	3.78
	intralobar tailored resection	107.67	4.60
	multilobar tailored resection	90.26	5.04
	AHE	109.00	8.14
	standard temporal resection ± AHE	102.33	3.81
	temporal tailored resection + AHE	108.51	5.12
24 mo	lesionectomy	109.57	3.70
	intralobar tailored resection	105.04	4.40
	multilobar tailored resection	97.71	7.11
	AHE	112.00	8.14
	standard temporal resection ±AHE	107.10	3.81
	temporal tailored resection + AHE	94.63	5.00
60 mo	lesionectomy	109.66	4.32
	intralobar tailored resection	108.32	5.36
	multilobar tailored resection	93.78	4.22
	AHE	105.16	9.25
	standard temporal resection ±AHE	114.03	5.64

Note. AHE = amygdalohippocampectomy, mo = months post-surgery, pre = presurgical evaluation

Seizure outcome:

Table 8 : Estimated marginal means and standard errors for Inhibition in standard scores for every evaluation time and for every seizure outcome group

Time	Engel	Mean	*SE*
pre	0	100.45	1.82
6 mo	1a	103.12	2.04
	> 1a	102.96	4.06
12 mo	1a	103.06	2.09
	> 1a	101.30	5.58
24 mo	1a	103.91	2.11
	> 1a	108.78	3.81
60 mo	1a	105.13	3.08
	> 1a	104.18	3.16

Note. Mo = months post-surgery, Engel = seizure outcome expressed in Engel categories

ASM load:

Table 9 : Estimated marginal means and standard errors for Inhibition in standard scores for every evaluation time and for every antiseizure drug load group

Time	ASM	Mean	*SE*
pre	1	102.93	3.26
	> 1	100.39	1.92
6 mo	1	104.27	2.24
	> 1	102.33	2.60
12 mo	1	104.21	2.41
	> 1	101.40	2.80
	0	105.47	6.99
24 mo	1	106.23	2.42
	> 1	102.02	3.29
	0	105.07	3.42
60 mo	1	106.84	2.98
	> 1	99.04	3.89
	0	108.98	5.29

Note. Pre = presurgical evaluation, mo = months post-surgery, ASM = number of antiseizure drugs

8.9. Appendix 9

Analyses of Executive Function Flexibility

Side of surgery:

Table 1 : Estimated marginal means in scaled score points and standard errors for each evaluation time and for every side of surgery, in Flexibility

Time	hemisphere	Mean	*SE*
pre	right	9.05	0.67
	left	10.55	0.63
6 mo	right	9.40	0.91
	left	10.56	0.72
12 mo	right	9.17	0.73
	left	11.20	0.64
24 mo	right	8.88	0.74
	left	11.40	0.68
60 mo	right	8.67	1.78
	left	9.93	1.24

Note. Pre = persurgical evaluation, mo = months post-surgery

Etiology:

Table 2 : Estimated marginal means in scaled score points and standard errors for time for each etiology group and for every evaluation time, in Flexibility

Time	etiology	Mean	*SE*
pre	MCD	9.13	0.85
	tumor	10.86	0.72
	dual pathology	7.60	1.02
	vascular malformation	8.00	2.97
	gliosis	11.39	1.29
	mesial temporal sclerosis	16.00	2.97
6 mo	MCD	8.73	0.91
	tumor	11.97	1.13
	dual pathology	9.87	1.21
	vascular malformation	10.00	2.97
	gliosis	8.30	1.56
	mesial temporal sclerosis	14.00	2.97
12 mo	MCD	8.50	0.85
	tumor	11.32	0.76
	dual pathology	10.28	1.07
	gliosis	10.68	1.30
	mesial temporal sclerosis	15.00	2.97
24 mo	MCD	10.97	0.95
	tumor	11.29	0.80
	dual pathology	8.71	1.01
	gliosis	8.38	1.40
	mesial temporal sclerosis	13.00	2.97
60 mo	MCD	8.77	1.26
	tumor	11.33	1.83
	dual pathology	8.00	2.97

Note. Pre = presurgical evaluation, mo = months post-surgery, Time = timing of perisurgical evaluation, MCD = malformation of cortical development

Type of surgery :

Table 3 : Estimated marginal means and standard errors in Flexibility in scaled score points for every type of surgery group for all evaluation times

Time	type of surgery	Mean	SE
pre	lesionectomy	10.26	1.02
	intralobar tailored resection	9.94	0.74
	multilobar tailored resection	9.96	1.18
	standard temporal resection ± AHE	7.10	1.38
	temporal tailored resection + AHE	11.48	1.48
6 mo	lesionectomy	11.76	1.51
	intralobar tailored resection	10.54	1.01
	multilobar tailored resection	8.29	1.59
	standard temporal resection ±AHE	9.67	1.31
	temporal tailored resection + AHE	9.56	1.38
12 mo	lesionectomy	11.05	1.11
	intralobar tailored resection	9.76	0.79
	multilobar tailored resection	8.96	1.24
	standard temporal resection ± AHE	11.50	1.31
	temporal tailored resection + AHE	10.47	1.38
24 mo	lesionectomy	10.68	1.06
	intralobar tailored resection	10.40	0.83
	multilobar tailored resection	7.82	1.42
	standard temporal resection ± AHE	10.17	1.31
	temporal tailored resection + AHE	11.24	1.64
60 mo	lesionectomy	10.92	1.64
	intralobar tailored resection	8.63	1.45
	multilobar tailored resection	8.00	3.21

Note. AHE = amygdalohippocampectomy, mo = months post-surgery, pre = presurgical evaluation

Table 4 : Overall F-test results of surgery type for every evaluation time for Flexibility

Time	F	$df_{Nom.}$	$df_{Denom.}$	p
pre	1.35	4	117	.26
6 mo	0.74	4	122	.57
12 mo	0.73	4	118	.58
24 mo	0.87	4	122	.48
60 mo	0.66	2	122	.52

Note. Mo = months post-surgery, pre = presurgical evaluation

Table 5 : Deviation contrasts in Flexibility between the mean of the cohort and the different type of surgery groups for every evaluation time in scaled score points

Note. pre = presurgical evaluaton, mo = months post-surgery, AHE = amygdalohippocampectomy

Time	type of surgery Deviation Contrasts	*Mean difference*	*SE*	*t*	*df*	*p*
pre	lesionectomy - Mean	0.51	0.95	0.54	96	.59
	intralobar tailored resection - Mean	0.19	0.78	0.24	95	.81
	multilobar tailored resection - Mean	0.21	1.06	0.20	89	.84
	standard temporal resection ± AHE - Mean	-2.65	1.19	-2.23	90	**.029**
	temporal tailored resection + AHE - Mean	1.74	1.26	1.38	101	.17
6 mo	lesionectomy - Mean	1.80	1.32	1.36	122	.18
	intralobar tailored resection - Mean	0.58	1.00	0.58	121	.56
	multilobar tailored resection - Mean	-1.67	1.37	-1.22	120	.23
	standard temporal resection ± AHE - Mean	-0.30	1.19	-0.25	89	.80
	temporal tailored resection + AHE - Mean	-0.41	1.23	-0.33	97	.74
12 mo	lesionectomy - Mean	0.70	1.01	0.70	106	.49
	intralobar tailored resection - Mean	-0.59	0.81	-0.72	101	.47
	multilobar tailored resection - Mean	-1.39	1.10	-1.26	95	.21
	standard temporal resection ± AHE - Mean	1.15	1.14	1.01	82	.32
	temporal tailored resection + AHE - Mean	0.12	1.19	0.10	90	.92
24 mo	lesionectomy - Mean	0.62	1.00	0.62	104	.54
	intralobar tailored resection - Mean	0.34	0.86	0.40	110	.69
	multilobar tailored resection - Mean	-2.25	1.24	-1.81	113	.07
	standard temporal resection ± AHE - Mean	0.11	1.17	0.09	85	.93
	temporal tailored resection + AHE - Mean	1.18	1.39	0.85	114	.40
60 mo	lesionectomy - Mean	1.74	1.60	1.08	104	.28
	intralobar tailored resection - Mean	-0.55	1.54	-0.36	102	.72
	multilobar tailored resection - Mean	-1.18	2.26	-0.52	83	.60

Table 6 : Pairwise comparisons of Flexibility in standard score differences for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each type of surgery group.

type of surgery	Time Pairwise Comparisons	*Mean difference*	*SE*	*t*	*df*	*p*
lesionectomy	pre - 6 mo	-1.50	1.48	-1.01	81	.31
	pre - 12 mo	-0.80	1.06	-0.75	77	.46
	pre - 24 mo	-0.42	1.08	-0.39	86	.70
	pre - 60 mo	-0.66	1.78	-0.37	120	.71
	6 mo - 12 mo	0.71	1.57	0.45	83	.65
	12 mo - 24 mo	0.37	1.12	0.33	81	.74
	24 mo - 60 mo	-0.24	1.80	-0.14	120	.89
intralobar tailored resection	pre - 6 mo	-0.60	1.01	-0.59	84	.55
	pre - 12 mo	0.17	0.77	0.23	79	.82
	pre - 24 mo	-0.47	0.86	-0.54	90	.59
	pre - 60 mo	1.31	1.57	0.83	122	.41
	6 mo - 12 mo	0.77	1.05	0.74	84	.46
	12 mo - 24 mo	-0.64	0.87	-0.74	83	.46
	24 mo - 60 mo	1.77	1.57	1.13	121	.26
multilobar tailored resection	pre - 6 mo	1.67	1.57	1.06	84	.29
	pre - 12 mo	1.00	1.20	0.83	79	.41
	pre - 24 mo	2.14	1.40	1.54	82	.13
	pre - 60 mo	1.96	3.42	0.57	80	.57
	6 mo - 12 mo	-0.67	1.61	-0.42	83	.68
	12 mo - 24 mo	1.15	1.37	0.84	76	.40
	24 mo - 60 mo	-0.19	3.51	-0.05	85	.96
standard temporal resection ± AHE	pre - 6 mo	-2.57	1.26	-2.05	74	**.044**
	pre - 12 mo	-4.40	1.26	-3.51	74	**.001**
	pre - 24 mo	-3.07	1.26	-2.44	74	**.017**
	6 mo - 12 mo	-1.83	1.18	-1.55	73	.13
	12 mo - 24 mo	1.33	1.18	1.13	73	.26
temporal tailored resection + AHE	pre - 6 mo	1.93	1.46	1.32	79	.19
	pre - 12 mo	1.01	1.46	0.69	79	.49
	pre - 24 mo	0.24	1.77	0.14	84	.89
	6 mo - 12 mo	-0.91	1.35	-0.68	77	.50

12 mo - 24 mo	-0.77	1.56	-0.50	77	.62

Note. pre = presurgical evaluaton, mo = months post-surgery, AHE = amygdalohippocampectomy

Table 7 : Overall F- test results of surgery type for every evaluation time in Flexibility

Time	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
pre	0.56	4	114	.69
6 mo	1.08	4	122	.37
12 mo	1.14	4	122	.34
24 mo	1.83	4	122	.13
60 mo	2.11	2	122	.13

Note. pre = presurgical evaluaton, mo = months post-surgery

Localization :

Table 8 : Overall F-test results of time for every localization group in Flexibility

region	*F*	$df_{Nom.}$	$df_{Denom.}$	*p*
frontal	0.78	4	97	.48
temporal	1.15	3	79	.34
parietal	1.19	4	86	.32
occipital	1.50	3	75	.22
multilobar	0.71	4	84	.59

Table 9 : Estimated marginal means in scaled score points and standard errors for every localization group for each evaluation time, in Flexibility

Time	localization	Mean	SE
	frontal	9.03	0.91
	temporal	9.84	0.72
pre	parietal	10.07	1.53
	occipital	12.00	1.81
	multilobar	9.96	1.15
	frontal	9.85	1.21
	temporal	9.90	0.81
6 mo	parietal	13.25	1.95
	occipital	11.04	2.06
	multilobar	8.22	1.58
	frontal	9.16	1.07
	temporal	10.98	0.69
12 mo	parietal	12.20	1.70
	occipital	10.00	1.81
	multilobar	8.98	1.22
	frontal	10.53	1.01
	temporal	10.70	0.70
24 mo	parietal	14.41	2.53
	occipital	8.04	2.06
	multilobar	7.82	1.41
	frontal	8.30	1.31
60 mo	parietal	13.06	2.00
	multilobar	8.00	3.14

Note. Pre = presurgical evaluation, mo = months post-surgery

Table 10 : Pairwise comparisons of Flexibility in scaled score points for each postsurgical evaluation compared to the presurgical evaluation and for consecutive evaluations, for each surgical localization group.

localization	Time Pairwise Comparisons	Mean difference	*SE*	*t*	*df*	*p*
	pre - 6 mo	-0.82	1.24	-0.66	87	.51
	pre - 12 mo	-0.13	1.06	-0.12	80	.90
	pre - 24 mo	-1.50	1.06	-1.41	88	.16
frontal	pre - 60 mo	0.73	1.53	0.48	121	.64
	6 mo - 12 mo	0.70	1.39	0.50	90	.62
	12 mo - 24 mo	-1.37	1.13	-1.21	80	.23
	24 mo - 60 mo	2.22	1.54	1.44	122	.15
	pre - 6 mo	-0.06	0.83	-0.07	79	.94
	pre - 12 mo	-1.14	0.72	-1.59	76	.12
temporal	pre - 24 mo	-0.86	0.76	-1.13	84	.26
	6 mo - 12 mo	-1.08	0.80	-1.34	77	.18
	12 mo - 24 mo	0.28	0.72	0.39	79	.70
	pre - 6 mo	-3.18	1.93	-1.65	81	.10
	pre - 12 mo	-2.13	1.65	-1.29	79	.20
	pre - 24 mo	-4.34	2.53	-1.71	81	.09
parietal	pre - 60 mo	-2.99	2.17	-1.37	110	.17
	6 mo - 12 mo	1.05	1.97	0.53	76	.60
	12 mo - 24 mo	-2.21	2.57	-0.86	78	.39
	24 mo - 60 mo	1.35	2.75	0.49	86	.62
	pre - 6 mo	0.96	1.97	0.49	76	.63
	pre - 12 mo	2.00	1.70	1.18	72	.24
occipital	pre - 24 mo	3.96	1.97	2.01	76	**.048**
	6 mo - 12 mo	1.04	1.97	0.53	76	.60
	12 mo - 24 mo	1.96	1.97	1.00	76	.32
	pre - 6 mo	1.75	1.59	1.10	84	.28
	pre - 12 mo	0.99	1.22	0.81	79	.42
	pre - 24 mo	2.14	1.42	1.51	82	.13
multilobar	pre - 60 mo	1.96	3.34	0.59	83	.56
	6 mo - 12 mo	-0.76	1.63	-0.47	84	.64
	12 mo - 24 mo	1.15	1.39	0.83	76	.41
	24 mo - 60 mo	-0.18	3.44	-0.05	88	.96

Note. pre = presurgical evaluation, mo = months post-surgery, bold print = significant result

Seizure outcome :

Table 11 Estimated marginal means and standard errors for Flexibility in scaled score points for every evaluation time and for every seizure outcome group

Time	Engel	Mean	*SE*
pre	0	9.90	0.47
6 mo	1a	10.37	0.69
	> 1a	9.41	0.96
12 mo	1a	10.16	0.57
	> 1a	10.77	0.82
24 mo	1a	10.14	0.66
	> 1a	10.66	0.77
60 mo	1a	7.47	1.52
	> 1a	11.35	1.83

Note. Mo = months post-surgery, Engel = seizure outcome expressed in Engel categories

ASM load:

Table 12 : Estimated marginal means and standard errors for Flexibility in scaled score points for every evaluation time and for every antiseizure drug load group

Time	ASM	Mean	*SE*
pre	0	10.58	2.76
	1	10.10	0.76
	> 1	9.72	0.57
6 mo	1	10.43	0.83
	> 1	9.58	0.78
12 mo	0	12.63	1.54
	1	10.28	0.65
	> 1	9.96	0.75
24 mo	0	10.41	0.78
	1	10.66	0.74
	> 1	9.49	1.24
60 mo	0	10.44	1.85
	1	7.50	2.27
	> 1	8.73	2.10

Note. Pre = presurgical evaluation, mo = months post-surgery, ASM = number of antiseizure drugs

9. Curriculum Vitae

PERSONALIEN	
Name und Vornamen	Kämpf, Marion Ingeborg Madeleine
Geburtsdatum	17.12.1983
Geburtsort	Strasbourg, Frankreich
Staatsangehörigkeit	Deutsch, Französisch
Familienstand	Ledig, 2 Kinder (Jahrgänge 2013 und 2015)

SCHULISCHER WERDEGANG	
1990-1994	Grundschule Sundheim, Kehl
1994-2003	Einstein Gymnasium, Kehl
24. Juni 2003	Abitur (Note 1,0) Baccalauréat (frz. Abitur, Note 17,6 Mention très bien avec les félicitations du jury)

UNIVERSITÄRER WERDEGANG	
WS 03/04	Studium 1. und 2. Semester Internationales BWL, Universität Mannheim
WS 04/05	Studium 1. und 2. Semester B.Sc. Psychologie Université Jules Vernes, Amiens, Frankreich
WS 05/07	Studium B.Sc. Psychologie, Université de Franche-Comté, Besançon, Frankreich
27. Juni 2007	Abschluss des Bachelor of Science Psychologie (Note 17,2 – ECTS-Grade A- Hervorragend, Jahrgangsbeste).
WS 07/08	Master 1 Psychologie, Université Victor Segalen Bordeaux II, Frankreich.
WS 08/09	Master of Science 2 Psychologie, Spécialité Neuropsychologie, Université de Savoie, Chambéry, Frankreich.
28. Juni 2009	Abschluss des Masters of Science Psychologie (Note 15,8 – ECTS-Grade B – Sehr gut).

BERUFLICHER WERDEGANG

1.August 2009 – heute	Psychologin am Epilepsiezentrum der Diakonie Kork, Klinik für Kinder und Jugendliche.
6. September 2018- heute	Leitende Psychologin der Klinik für Kinder und Jugendliche, Diakonie Kork.
WS 2013- 2016	Fortbildung in kognitiver Verhaltenstherapie, ACCE und AFTCC Paris-Nancy-Metz, Frankreich.

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11. Eidesstattliche Versicherung

1. Bei der eingereichten Dissertation zu dem Thema „Executive functions in children and adolescents after epilepsy surgery – analysis of long-term outcome and possible predictors" handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

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