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Recovery of Consciousness during the Postictal State in Frontal and Temporal Lobe Epilepsy

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Abstract

This doctoral study investigates the time that people diagnosed with temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) need to give a first adequate response (FAR) during the postictal state of focal seizures as a first sign in the process of recovering consciousness (RC); it also examines the variables that could influence the time required to be able to answer the cognitive and behavioral evaluation. A quantitative research design was chosen using a descriptive and correlational approach to determine durations, identify characteristics, and correlate variables. The analyzed variables were the clinical features and the characteristics of the epileptic seizures.

A retrospective investigation was performed on data of patients examined from March 2006 to December 2018 at the Epilepsy Monitoring Unit at the Hospital of the Ludwig-Maximilians University of Munich. A total of 188 patients and 332 epileptic seizures met the inclusion criteria. Patients were divided into four groups according to the localization of the epileptic seizure onset: right temporal lobe epilepsy (RTLE, n = 66), left temporal lobe epilepsy (LTLE, n = 85), right frontal lobe epilepsy (RFLE, n = 18), and left frontal lobe epilepsy (LFLE, n = 19).

Patients with LTLE required 106.8 ± 93.7 seconds (range, 5 to 323 seconds) to recover consciousness during the postictal state and be able to respond to the cognitive and behavioral testing and with RTLE 60.9 ± 48.3 seconds (range, 7 to 239 seconds). Frontal lobe patients with left-sided lateralization needed 54.2 ± 66.6 seconds (range, 6 to 280 seconds) and with right-sided lateralization 68.6 ± 90.5 seconds (range, 8 to 342 seconds) to recover consciousness during the postictal state. In conclusion, left temporal lobe seizure onset can be used as a localizing indicator in the recovering process of consciousness during the postictal state, in temporal lobe epilepsy the duration is longer and in frontal lobe epilepsy the duration to respond is shorter.

Zusammenfassung

Die vorliegende Dissertation erforscht die Zeit, die Patienten mit Temporallappen-Epilepsie (TLE) und Frontallappen-Epilepsie (FLE) benötigen, um eine erste angemessene Antwort während des postiktales Zustandes nach fokalen Anfällen geben können. Diese Antwort wird als erstes Zeichen im Prozess des Wiedererlangens des Bewusstseins genommen. Außerdem wurden Variablen der kognitiven und verhaltensbezogenen Testung, die die Zeit beeinflussen können, untersucht. Ein quantitatives Forschungsdesign wurde ausgewählt, bei dem ein deskriptiver und korrelierender Ansatz verwendet wurde, um die Zeit bis zur ersten angemessenen Antwort zu bestimmen, und diese mit klinischen Merkmalen des Patienten und die Eigenschaften der epileptischen Anfälle zu korrelieren.

Die retrospektive Studie wurde für Patientendaten von März 2006 bis Dezember 2018 aus der Epilepsie-Monitoring-Einheit des Klinikums der Ludwig-Maximilians-Universität München durchgeführt. Insgesamt 188 Patienten und 332 epileptische Anfälle erfüllten die Einschlusskriterien. Die Patienten wurden nach der Lokalisation des epileptischen Anfallsbeginns in vier Gruppen eingeteilt: Temporallappenepilepsie rechts (RTLE, n = 66), Temporallappenepilepsie links (LTLE, n = 85), Frontallappenepilepsie rechts (RFLE, n = 18) und Frontallappenepilepsie links (LFLE, n = 19).

Patienten mit LTLE benötigten 106,8 ± 93,7 Sekunden (Range, 5 bis 323 Sekunden), um im postiktalen Zustand das Bewusstsein wiederzuerlangen und auf die kognitiven und Verhaltensanweisungen reagieren zu können, und Patienten mit RTLE benötigen 60,9 ± 48,3 Sekunden (Range, 7 bis 239 Sekunden). Frontallappenpatienten mit linksseitiger Lateralisation benötigten 54,2 ± 66,6 Sekunden (Range, 6 bis 280 Sekunden) und mit rechtsseitiger Lateralisation 68,6 ± 90,5 Sekunden (Range, 8 bis 342 Sekunden), um das Bewusstsein während des postiktalen Zustandes wiederzuerlangen. Als Schlussfolgerung lässt sich festhalten, dass der Beginn eines epileptischen Anfalls im linken Temporallappen eine längere Phase der Wiedererlangung des Bewusstseins beginnt. Dies kann als lokalisierendes Zeichen verwendet werden.

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List of Abbreviations

AED	Antiepileptic Drugs
DRE	Drug-resistant Epilepsy
EMU	Epileptic Monitoring Unit
FAR	First Adequate Respond
FLE	Frontal Lobe Epilepsy
GTCS	Generalized tonic-clonic seizure
LFLE	Left Frontal Lobe Epilepsy
LMU	Ludwig Maximilian University München
LTLE	Left Temporal Lobe Epilepsy
MR	Mean Rank
RFLE	Right Frontal Lobe Epilepsy
RC	Recovering Consciousness
RTLE	Right Temporal Lobe Epilepsy
s	Seconds
TFAR	Time to give the First Adequate Response
TRC	Time in Recovering Consciousness
TLE	Temporal Lobe Epilepsy

Chapter 1. Introduction

Consciousness enables our experience through life and determines our capacity to interact with the environment. Transient loss of consciousness makes it impossible for affected people to respond to their surroundings and take care of themselves, causing direct consequences for safety, productivity, emotional health, and quality of life. Some neurological diseases, such as epilepsy, cause loss of consciousness during the epileptic seizures commonly. In some cases loss of consciousness remains seconds or minutes after the seizure during the postictal state, therefore for epileptologists, consciousness is an important concept used for the classification of epileptic seizures. Epilepsy is characterized by the repeated and unpredictable occurrence of seizures that involve the sudden and recurrent interruption of normal brain functions through rhythmic and synchronous activity of neuronal populations (Noebels et al., 2010) originating in cortical and subcortical regions, the so-called epileptogenic zones (Lüders et al., 1992). The recurrent interruption of normal brain function causes loss of consciousness and can have cognitive, behavioral, and physical manifestations that may continue long after the seizure has ended during the so called postictal state (Fisher & Engel, 2010; Rémi & Noachtar, 2010; Schmidt & Noachtar, 2010).

The signs and symptoms that are presented during the postictal state has been used in the diagnosis and classification of epilepsy, as a tool to differentiate epilepsy from other neurological diseases and psychiatric disorders, and to understand how epilepsy affects quality of life (Schmidt & Noachtar, 2010). The few descriptions of postictal characteristics have helped physicians to diagnose and distinguish epileptic seizures from non-epileptic attacks (Rèmi & Noachtar, 2010), to characterize seizure subtypes, to localize the epileptogenic zone, to understand the causes of cognitive deficits in focal epilepsies (Helmstaedter et al., 1994) and to predict postoperative memory function (Vulliemoz et al., 2012)

Furthermore, epilepsy is a disease associated with significant psychological consequences – including increased levels of anxiety, depression, and poor self-esteem. Besides, it has important economic repercussions in terms of affecting the health care system and loss of labor productivity among others (Botero & Uribe, 2010; Kwan et al., 2010; Moog, 2009; Sisodiya et al., 2002). Studies that explore quality of life indicate that people with epilepsy have a lower quality of life in comparison to people with other chronic illness or healthy people (Charidimou & Selai, 2011).

The mechanisms of recovering consciousness during the postictal state has not been unveiled yet. Questions regarding the reasons why some people with epilepsy remain unconscious after a focal seizure, while others recover consciousness right after the ictal state – or the sequence of events influencing the duration of the recovery process of consciousness in the postictal state - are still under investigation. Clear description of the different levels of consciousness and the recovery process of consciousness after an epileptic seizure are important to understand neuropsychological, clinical, and practical consequences for the treatment of persons with epilepsy (Avanzini, 2013) and improve patient management and quality of life.

1.1. Aim of this study

People with epilepsy feel that impairment of consciousness affects their quality of life. After an epileptic seizure, not knowing when they will recover consciousness, increases their anxiety. Being able to explain to people with epilepsy and their families what to expect during the postictal state and the time they will likely require giving a first adequate response could help to plan what they can do and feel more empowered.

Up until now, the structures that are affected during impairment of consciousness have been investigated, but the causes of variance in the recovery of consciousness remain an open question. The factors that play a main role in the recovery of consciousness during the postictal state and the lateralization significance need to be investigated as well. Only seizures, that remained focal, i.e. that did not evolve into secondarily generalized tonic-clonic seizures (GTCS) were included to be able to address the differences in the hemispheres and lobes without the possible influence of having all brain structures affected during a GTCS.

Herein the research addresses four major questions:

1. How much time do people with temporal lobe epilepsy and frontal lobe epilepsy need to give a first adequate response during the postictal state?

2. Can the time that people with epilepsy require to give the first adequate response during the postictal state be used as a lateralizing sign?

3. Do the clinical characteristics of patients with epilepsy affect the duration of regaining consciousness during the postictal state?

4. Do the characteristics of the epileptic seizure influence the duration of the recovery of consciousness among patients with epilepsy?

To answer these questions the aim of this study is to investigate the duration that patients with temporal lobe epilepsy and frontal lobe epilepsy need to give the first adequate response during the postictal state, as the first sign in the process of recovering consciousness after an epileptic seizure. Studying the time people with temporal and frontal lobe epilepsy require to give a first adequate response during the postictal state is intended to understand the recovering process of consciousness, evaluate their lateralizing significance and determine the factors that impact the ability to recover consciousness during postictal state. Finally, to contribute to the debate of the significance of impairment of consciousness in people with epilepsy.

Chapter 2. Literature review

Epileptic convulsions can be understood, as
'the result of experiments made by disease on the brain of man'.
(John Hughlings Jackson, 1875).

2.1. Epilepsy and Epileptic Seizures

2.1.1. Epidemiology and Definition of Epilepsy and Epileptic Seizures

According to the 2019 update of the WHO's Global Burden of Disease Study in collaboration with the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) between 50 and 65 million people have epilepsy and around 80% of them live in developing countries. Epilepsy contributes 0.6% of the global burden of diseases. Nearly 5% of the world population will have one seizure in their life. An estimated of 2.4 million people are diagnosed with epilepsy each year (30 – 50 per 100.000 people). In developed countries the incidence of epilepsy is 24 – 53/100.000 persons/year and in developing countries is 26 – 70/100.000 persons/year. According to age, sex, race, epileptic syndrome, and socioeconomic status, researchers have observed the highest incidence rates in children under one year and in adults over 65 years of age (Panayiotopoulos, 2010; WHO, 2019) and is associated with a mortality risk two to five times greater than the general population (Neligan et al., 2010).

Prevalence rate could be lower documented, because of the negative social consequences for people with epilepsy and their families (Chin, 2012; Yemadje et al., 2011). Studies indicate that the rates of epilepsy prevalence are generally higher in low- and middle-income countries and in low-income-population classes in developed countries, so it could be inferred that poverty and poor health conditions represent a substantial public health burden (Ngugi et al., 2011). Hirtz et al. (2007) report a prevalence of epilepsy in 700 per 100.000 persons. The prevalence could increase with the aging of the elderly population triggered by structural lesions and degenerative changes in the brain (Brodie et al., 2009).

According to the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) epilepsy can be define as

> *"a disorder of the brain characterized by enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences of this condition"*

and an *epileptic seizure* as

> *"a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain"* (Fisher et al., 2005, p.471).

In clinical practice, physician diagnose epilepsy based on the following condition:

> *"(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"* (Fisher et al., 2014, p. 477).

ILAE and IBE decided that the term *disease* is more appropriate instead of *disorder* in the classification of epilepsy. The expression disorder implies that epilepsy can be *resolved* and has the connotation of "only temporality", but there is no guarantee that there will not be reoccurrence (Fisher et al., 2014). Epilepsy is now considered 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 at least 10 years, with no medicines for the last 5 years"* (Fisher et al., 2014, p.477).

2.1.2. Classification of Epileptic Seizures

Seizures are the core symptom of epilepsy. Epilepsies are diverse, so are seizures. Depending on where in the brain the pathological neuronal activity is taking place, the symptomatology, or semiology, of the seizure may be very different, from subtle jerks over pure loss of consciousness to the prototypical generalized tonic-clonic seizure. Since certain seizure types are associated with certain epilepsy syndromes and a syndrome of different seizure may be defining for an epilepsy, it is necessary to have a classification system, that enables naming seizures on a common basis, that all physicians can refer to. Unfortunately for clinical practice, there are two competing classification systems, the one proposed by the ILAE (Fisher et al., 2017a) and the "semiological seizure classification system" (Lüders et al., 1998) proposed by epilepsy surgery

centers. In this study, the latter will mostly be used, because it is applied in the EMU of the LMU for the reason of being an epilepsy surgery center and only the semiological classification will yield the necessary information from the patients´ seizures. The ILAE classification is widely used, therefore it will also be presented when necessary. The aim of this study cannot be a dissection of the two classification systems and is focused on the postictal period. Therefore, sometimes the ILAE classification (especially of syndromes) and sometimes the semiological classification needs to be referenced.

2.1.2.1. ILAE Classification of Epileptic Seizures and Epilepsy

In 1981 the ILAE developed a classification of epilepsy and epileptic seizures that was widely accepted. Subsequently, the ILAE presented reclassification reports in 1989, 2001, 2006 and 2010 based on the new semiological and electroclinical findings. In 2017, a new classification was released to standardize the description of the diagnosis and facilitate the development of hypotheses and therapeutic strategies. The diagnostic levels are described by Engel (2001) and Scheffer et al. (2017):

Level 1: Determine epileptic seizure

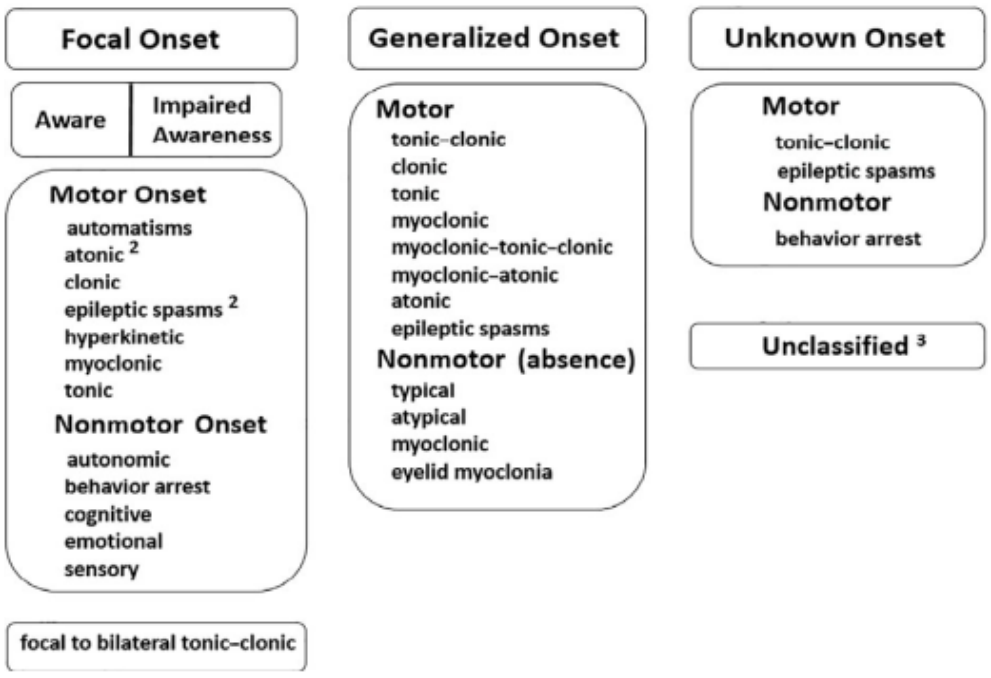
Clinicians verify that the paroxysmal event is an epileptic seizure if it is possible with support from EEG.

Level 2: Epileptic seizure type

The epileptic seizure can be grouped according to the epileptic discharge onset zone and the neuronal networks involved in the propagation patterns in three categories and further sub-categories according to ictal semiology in *focal seizures* delimited to one hemisphere and can secondary spread to brain regions of both hemispheres. Focal seizures are first classified by determining the *level of* awareness (aware or impaired awareness) throughout the seizure and, second by sub-grouping according to the first symptoms and signs of the seizure in motor (automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic or tonic) or nonmotor (automatic, behavior arrest, cognitive, emotional or sensory) onset. If the focal seizure propagates to both hemispheres it is classified as "focal to bilateral tonic-clonic". In generalized seizures originate at some point in the brain and rapidly spread to both hemispheres, can include cortical and subcortical structures. The location and lateralization are not consistent from one seizure to another; thus, seizures can be asymmetric. Impairment of awareness is common

in these types of seizures. These are subgrouped in motor (tonic-clonic, clonic, tonic, myoclonic, myoclonic-tonic-clonic, myoclonic atonic, atonic, or epileptic spasms) or nonmotor seizures, known as absence, (typical, atypical, myoclonic or eyelid myoclonia). And in **unknown seizure onset**, the seizure onset is not possible to be determine, can also be classified in *motor* (tonic-clonic or epileptic spasms) or *non-motor* (behavior arrest) (Bagshaw & Cavanna, 2011; Berg et al., 2010; Blume et al., 2001; Bagshaw & Cavanna, 2011; Fisher et al., 2017a) (figure 1).

Figure 1. ILAE Classification of Seizure Types



[2] Degree of awareness usually is not specified. [3] Due to inadequate information or inability to place in other categories.
From: "Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology" by Fisher et al., 2017a, Epilepsia, 58(4): 522-530, Figure 2 (doi: 10.1111/epi.13670)

It is possible that the seizure onset zone causes no clinical symptoms, but if the epileptic activation reaches other cortical or subcortical regions certain clinical symptoms will show up and the seizure can be classified (Noachtar, 2004). Approximately 60 - 70% of patients with epilepsy have focal seizures and 30 - 40% generalized seizures (Bancand et al., 1981). Over 70% of patients with partial epilepsy occasionally experience secondarily generalized seizure (Forsgren et al., 1996).

Level 3: Syndrome

Epilepsy syndromes are determined by a group of distinctive and recognizable clinical patterns (age of onset, usual course, types of seizures, genetic information, localization) and EEG features (part of the brain involved) that usually occur together. Specific syndromes commonly have their onset in childhood, such as childhood absence epilepsy (0.8 per 100.000 persons), juvenile myoclonic epilepsy (0.7 per 100.000 persons), and benign rolandic epilepsy (2.8 per 100.000 persons) (Neligan et al., 2010). It is understood that a syndromic diagnosis may not always be possible. The syndromic diagnosis derived from a list of accepted epilepsy syndromes (Bancand et al., 1981; Engel, 2001, 2006).

Level 4: Etiology of the Epilepsy

Causes and risk factors of epilepsy vary considerably from population to population and a patient can fall within more than one etiological category. The etiologies of epilepsy can be categorized as ***structural,*** which refers to abnormalities visible in neuroimaging as the cause of the patients seizures that can be genetic (malformations of cortical development), acquired (stroke, head trauma, infection), or both; ***genetic*** as consequence of a known or presumed genetic mutation that begins mostly in childhood where the neurological examination is normal, the response to treatment is good and has characteristic patterns on EEG; ***infectious*** as an results from a known infection of the nervous system, including bacterial, fungal, parasitic, and viral varieties; ***metabolic*** denotes a well delineated metabolic defect with biochemical changes through the body; ***immune*** is a direct result from an autoimmune-mediated central nervous system inflammation (e.g. neurocysticercosis); and ***unknown***, the cause is not possible to determine (Bruno et al., 2013; Scheffer et al., 2017; Vezzani et al., 2016;).

Level 5: Impairment

Impairment is an optional designation of the degree of impairment caused by the epileptic condition. Classification of impairment will be derived from the World Health Organization ICIDH-2 International Classification of Functioning, Disability and Health (see WHO, 2001).

2.1.2.2. Semiological Classification of Epileptic Seizures defined by Lüders

Lüders et al. (1998) propose a classification based on ictal semiology to avoid some confusions that they considered existed in the ILAE classification, where the distinctions of epileptic syndromes and epileptic seizures were described as being not clear cut enough. They emphasize that the classification of epileptic seizures should be based exclusively on semiology, while classification of epilepsies should be based on the clinical profile (seizures, clinical history, neurological examination, EEG, neuroimaging, and other information needed relating to the disease), and not including the syndrome (namely "focal" or "generalized") in the seizure classification as this information may not be available. This classification is not congruent with the ILAE-classification but takes an approach that is more typical to the clinical classification of diseases (Palmini et al., 2020), especially in the setting of a presurgical epilepsy evaluation, where no presumptions about the underlying syndrome should cloud the analysis of the seizures, because finding the epileptogenic zone is exactly the goal of that evaluation.

Based on ictal semiology Lüders et al. (1998) categorized epileptic seizures in four *"spheres"*:

a. *Sensorial sphere:* Seizures that affect exclusively the sensory area are called *aura*. An aura can be *somatosensory* if it consists of abnormal somatosensory sensation, *auditory* by isolated auditory hallucinations or illusions, *olfactory* by perception of a smell, *visual* by visual isolated hallucinations or illusions, *gustatory* by perception of a taste as an epileptic phenomenon, *autonomic* by activation of autonomic cortical centers, *abdominal* by abdominal sensations (patients with temporal lobe epilepsy frequently have this kind of aura) and *psychic* by complex hallucinations and illusions that usually affect different senses.

b. *Consciousness sphere:* Seizures that produces an alteration of consciousness are known as dialeptic seizure. The authors classify altered consciousness as the ILAE classification does as episodes of unresponsiveness or decreased responsiveness that are not associated with motor alterations. To establish the diagnosis of dialeptic seizures amnesia of the episode is necessary.

c. *Autonomic sphere:* To make the diagnosis of autonomic seizure, autonomic episodes must be documented by appropriate polygraphic recording (tachycardia, blood pressure, palpitations changes or "hot flashes") or by direct observation. Patients are not always able to report autonomic symptoms.

d. ***Motor sphere:*** Seizures produced by motor manifestations can be subgrouped as simple motor seizures ("simple" and unnatural motor movements) and complex motor seizure (complex natural movements that are inappropriate for the situation). Simple motor seizure can be subdivided in myoclonic, tonic, clonic, tonic-clonic, versive seizure, and epileptic spasms. There are three types of complex motor seizure: hypermotor, automotor, and gelastic seizure, where awareness can be impaired or not.

Unclassified seizures are called *special seizures*, including primarily seizures characterized by "negative" motor signs such as atonic, astatic, akinetic, hypomotor, negative myoclonic and aphasic seizures. To this semiological classification Lüders et al. (1998) added the somatotopic distribution (left or right; bilateral asymmetric, axial, and generalized; left and right hemispheric). Furthermore, cases that include symptoms from two or more spheres, are classified by the predominant clinical manifestation (table 1).

Table 1. Semiological Seizure Classification

1. Epileptic seizure [b]		
2. Aura	2.1. Somatosensory aura [a]	
	2.2. Auditory aura [a]	
	2.3. Olfactory aura	
	2.4. Abdominal aura	
	2.5. Visual aura [a]	
	2.6. Gustatory aura	
	2.7. Autonomic aura	
	2.8. Psychic aura	
3. Autonomic seizure [b]		
4. Dialeptic seizure [a]	4.1. Typical dialeptic seizure	
5. Motor seizure [a,b]	5.1. Simple motor seizure [a]	5.1.1. Infantile spasms [a]
		5.1.2. Myoclonic seizure [a]
		5.1.3. Tonic-clonic seizure [a]
		5.1.4. Tonic seizure [a]
		5.1.5. Clonic seizure [a]
		5.1.6. Versive seizure [a]
	5.2. Complex motor seizure [b]	5.2.1. Hypermotor seizure [b]
		5.2.2. Automotor seizure [b]
		5.2.3. Gelastic seizure [b]
6. Special seizure	6.1. Atonic seizure [a]	
	6.2. Hypomotor seizure [b]	
	6.3. Negative myoclonic seizure [a]	
	6.4. Astatic seizure	
	6.5. Akinetic seizure [a,b]	
	6.6. Aphasic seizure [b]	
7. Paroxysmal event		

[a] Left/right/axial/generalized/bilateral asymmetric, [b] Left/right hemisphere
From: "Klassifikation epileptischer Anfälle und Syndrome" by Noachtar & Rémi, 2012, Nervenarzt 83:156-161, Table 2 (doi: 10.1007/s001115-011-3333-4)

The second step after describing single semiological signs is describing a possible sequence of semiology (e.g. abdominal aura -> hypermotor seizure).

2.1.3. Stages of an Epileptic Seizure

An epileptic seizure can be divided in four stages, not all have to be necessarily present: aura, ictal, postictal, and interictal. The first stage can appear as a sign that an epileptic seizure is about to happen, sometimes involving alterations in smell, taste, visual, perception, hearing and emotional state. Auras neurophysiologically have neuronal seizure activity and are often followed by clinical seizures with observable seizure signs. This second stage is known as the ictal period or as the seizure, which typically lasts seconds to a few minutes. This event has been well studied to help defining the epilepsy syndrome, antiepileptic medication, among other characteristics. Following the seizure, the person enters into the postictal state where the brain recovers from the active stage with highly variable time frames. Common symptoms experienced during this state are drowsiness, confusion, sleepiness, lethargy, anxiety, depression, aphasia, apraxia, exhaustion, headache, nausea, irritability, general weakness, or weakness in one part or side of the body. The last stage is known as interictal state (between seizures). If there is no postictal state and the person does not recover consciousness, it may evolve into status epilepticus (Fisher & Engel, 2010; Schmidt & Noachtar, 2009).

2.2. Epileptic Syndrome

As aforementioned, for the diagnosis of focal seizures the ILAE considers the semiology (i.e. auras, motor manifestations, autonomic response, impairment of consciousness), the hemispheric lateralization (which are signs and symptoms peculiar for each hemisphere), and the localization (frontal, temporal, parietal, or occipital). According to the location, temporal lobe epilepsy is the most common type of epilepsy in focal seizures, and frontal lobe epilepsy is second (Rasmussen, 1987; Sander et al., 1995).

The classification systems then additionally describe the etiology (e.g. hippocampal sclerosis, tumor, stroke, genetic). Finally, it is important to describe conditions related with the patient´s quality of life (e.g. memory lost, family history of seizures, cognitive deterioration, injuries, and so on) (Lüders et al., 1998; Noachtar & Rémi, 2012). These last two tiers of classification are not part of this study.

2.2.1. Temporal Lobe Epilepsy

Seizures in temporal lobe epilepsy (TLE) are often characterized by aura, altered consciousness, amnesia, and automatisms. Auras are known as simple focal seizures that can occur in isolation or evolve within seconds into an epileptic seizure. A rising epigastric sensation is the most common temporal lobe aura. Other occurring types of auras are auditory, olfactory, gustatory or experiential phenomena such as *jamais vu* and *déjà vu* (Blumenfeld et al., 2004; Fogarasi et al., 2007; Gloor et al., 1982; Pfänder et al., 2002; Sadler, 2006; Williamson et al., 1993).

In seizures, where the seizure activity remains lateralized, consciousness may be preserved, but in focal to bilateral and generalized seizures consciousness is typically impaired, as seizure activity in both hemispheres causes an abnormal synchrony in regions responsible for the maintenance of a state of consciousness (Bagshaw & Cavanna, 2011; Gloor et al., 1980; Inoue & Mihara, 1998). Altered consciousness affect perception, memory, cognition and voluntary motility (Berg, 2008; Danielson et al., 2011; Engel, 2001; Gloor, 1986). Furthermore, in preserved consciousness, verbal automatisms and hyperactive behavior is more frequently observed. In seizures with lateral temporal cortex onset of language dominant side, patients tended not to be aware of their seizures (Inoue & Mihara, 1998). Also, they can be unable to remember the seizure and what was happening before the event, retrograde and anterograde amnesia is variable (Halgren et al., 1985; Halgren & Wilson, 1985). Altered consciousness and following amnesia are accompanied by automatisms. Frequent automatisms engage hands or mouth, less common are crying, vocalization, affective behavior (like fear) and ictal speech (Blair, 2012; Penry & Dreifuss, 1969) (table 2).

Table 2. Semiological Features in TLE – Lateralizing or Localizing Value	
Feature	Localization
Automatism	
Unilateral limb automatism	Ipsilateral focus
Oral automatism	Medial temporal lobe
Unilateral eye blinks	Ipsilateral to focus
Postictal cough	Temporal lobe
Postictal nose wiping	Ipsilateral temporal lobe
Ictal spitting or drinking	Temporal lobe focus (right)
Gelastic seizures	Mesial temporal, hypothalamic, frontal (cingulate)
Dacrystic seizures	Mesial temporal, hypothalamic
Unilateral limb automatism	Ipsilateral focus
Whistling	Temporal lobe
Autonomic	
Ictal emeticus	Temporal lobe focus (right)
Ictal urinary urge	Temporal lobe focus (right)
Piloerection	Temporal lobe focus (left)
Motor	
Early nonforced head turn	Ipsilateral focus
Late version	Contralateral focus
Eye deviation	Contralateral focus
Focal clonic jerking	Contralateral perirolandic focus
Asymmetrical clonic ending	Ipsilateral focus
Fencing	Contralateral (supplementary motor)
Figure 4	Contralateral to the extended limb (temporal)
Dystonic limb posturing	Contralateral focus
Tonic limb posturing	Contralateral focus
Unilateral ictal paresis	Contralateral focus
Postictal Todd's paresis	Contralateral focus
Speech	
Ictal speech arrest	Temporal lobe (usually dominant hemisphere)
Ictal speech preservation	Temporal lobe (usually nondominant)
Postictal aphasia	Temporal lobe (dominant hemisphere)
From: "Temporal Lobe Epilepsy Semiology" by Blair, 2012, Epilepsy Research and Treatment, 1-10, Table 2. (doi:10.1155/2012/751510)	

Therapy begins typically with AEDs, but TLE patients become therapy-refractory in most cases. Then, the success rates for seizure freedom after epilepsy surgery in suitable candidates is 67-90%, especially for mesial TLE with hippocampal sclerosis. One year postoperatively 85% are still seizure free and 66% at 10 years (Rosenow & Lüders, 2001). Hippocampal sclerosis represents 80% of TLE causes (Williamson et al., 1993).

2.2.2. Frontal Lobe Epilepsy

The frontal lobes cover a large area of the brain where a wide range of functions are present such as language, cognition, motor and higher brain tasks causing a variety of signs and symptoms upon impairment. This makes the diagnosis of frontal lobe epilepsy (FLE) difficult, therefore it sometimes can be confused with nonepileptic seizures like psychogenic, movement disorders and parasomnias (Laskowitz et al., 1995). The seizures may be brief, can occur in sleep,

in clusters or series, with vocalization, ocular and head deviation. Motor manifestations and complex gestures are also a main characteristic (Bonini et al., 2014). Auras can be followed by proximal motor manifestations, typical – but not most common – are hypermotor activities (bicycle pedaling, laughing, thrashing of the extremities, shouting). When the seizure is short, the postictal state can be brief in some patients (Lüders et al., 1999; Manford et al., 1996). Gestural automatism includes disorganized or exploratory movements towards themselves or to the environment and more complex movements like flexion and extension of the fingers, crossing and uncrossing of the legs (Kochen, 2017). Spread of frontal lobe activity can cause epileptic automatism such as lip smacking (Gloor, 1990; Jasper, 1964). Scalp EEG can be non-diagnostic or even misleading as 40% of patients with frontal lobe seizures do not have any interictal discharges (Bautista et al., 1998; Salanova et al., 1993) and because of movement artifacts.

Clinical manifestations depend on frontal lobe localization (Inoue & Mihara, 1998; Lüders et al., 1999; Manford et al., 1996; O'Muircheartaigh & Richardson, 2012; Stuss, 2011):

Table 3. Semiological Features in Frontal Lobe Epilepsy

Localization	Signs and symptoms
Primary motor cortex	Can begin with tonic or myoclonic movement and propagate to other muscles according to the homunculus. Sensory symptoms can occur in isolation or in combination with other motor movements. Atonic seizures may appear.
Secondary motor cortex	Sudden onset and withdrawal of tonic and asymmetric postures that last 10 to 40 seconds, with minimal postictal confusion. Asymmetric postures of the upper limbs occur with the extension of the contralateral arm to the hemisphere from which the onset of the epileptic seizure and with flexion of the ipsilateral upper limb. The epileptic seizure begins with a loud vocal sounds or interruption of speech. Contralateral version of head and eyes.
Orbitofrontal cortex	Decrease level of consciousness, repetitive gestural automatisms, olfactory hallucinations, illusions and autonomous signs.
Frontopolar cortex	Intrusive thoughts, alterations of consciousness, and cephalic and ocular version ipsilateral at the beginning with possible progression of the version towards the contralateral hemisphere. Autonomic symptoms and axial rhythmic movements can lead to falls.
Dorsolateral cortex	Epileptic seizures in the dominant hemisphere that occur near Broca area can cause aphasia. There is no alteration of consciousness. Tonic motors signs with cephalic and ocular contralateral version. Intrusive thoughts and forced actions.
Cingulate cortex	Gestural automatisms with loss of consciousness at the beginning, affective auras and autonomic symptoms. In language nondominant seizure within extensive epileptogenic areas and patients with automatic behavior tend to be unaware of their seizures.
Frontoparietal operculum	Unilateral facial clonic movements (mouth and tongue), laryngeal symptoms, joint problems, masticatory or swallowing movements and hypersalivation. Sensory (epigastric), experiential (fear) and autonomic (urogenital, gastrointestinal, cardiovascular or respiratory) auras are common. Taste hallucinations can be frequent.

2.3. Consciousness in Epilepsy

2.3.1. Definition of Consciousness in Epilepsy

Consciousness is a continuum ranging across different states (Wade, 1996) that depends on the level of arousal and the capacity to respond to external stimuli. These two aspects were introduced as level of arousal and level of content of consciousness by Plum and Posner (1972). The level of arousal (wakefulness, alertness) has a range from adequate to no response to stimuli, is supported by structures in the brainstem (Laureys, 2005). The content represents a state of awareness (responsiveness) of subjective experience and the capacity to respond to different cognitive and motor tasks weighted towards specific higher-order information processing and sensory-motor, limbic or mnemonic functions (Bagary, 2011; Blumenfeld, 2012; Mann & Cavanna, 2011; Nagel, 1974; Plum & Posner, 2007; Pöppel, 1993). The frontoparietal cortex structure is related to the content of consciousness (Laureys, 2005). A focal lesion within either of these two networks can cause fractional loss of consciousness (Broderick et al., 1999).

The ILAE includes these two concepts in the new operational classification of seizure types, and define consciousness as a state of mind where subjective and objective elements are present such as "*sense of self as a unique entity, awareness, responsiveness, and memory*" (Fisher et al., 2017b).

In order to translate the ILAE definition of consciousness to daily clinical practice, responsiveness, awareness and memory will be described as follows:

- Responsiveness is the ability to appropriately react by movement or speech when a verbal or non-verbal stimulus is presented (Fisher et al., 2017b). Depending on the cause of the condition, time lapse, or effectiveness of medical management of the underlying cause consciousness can have different levels: normal (able to respond promptly and spontaneously to name, location and date/time), confused (no quick responds, is disoriented and has difficulties following instructions), delirious (disoriented, hallucinations/delusions, restlessness), drowsy (somnolent, sleepy), obtunded (slowed psychomotor responses and decreased interest in their surrounding), stuporous (no spontaneous activity, respond by grimacing or drawing away from painful stimuli), and comatose (no response to stimuli, no pupillary response) (Plum & Posner, 2007; Porth, 2007; Tindall, 1990). The Glasgow Coma Scale (GCS) is

the common scoring system to describe the level of consciousness in neurological pathologies (see www.glasgowcomascale.org) and in epilepsy the Ictal Consciousness Inventory (ICI) can be used (Cavanna et al., 2008).

- Awareness is defined as conscious perception of events and oneself, including cognition of life experiences and intentions. Awareness can be divided in knowledge of self as being distinct from others, own family, and social and cultural history, and knowledge of the environment as conscious perception through the sensory modalities (e.g. visual, auditory, somesthetic or olfactory perception) (Blumenfeld, 2012; Chalmers, 1996; Gastaut, 1970; Gosseries et al., 2011; Mann & Cavanna, 2011; Nagel, 1974).

- Memory can be defined as the capacity to recall events (e.g. the seizure), as well as words/phrases/information/time evaluated within at cognitive evaluation during and/or after the seizure (Fisher et al., 2017b; Gastaut, 1970).

Clinicians continue to use consciousness to make decisions about safety and legal issues such as driving privileges (Blumenfeld et al., 2015). To avoid misdiagnosis, temporary block of verbal or motor output has to be distinguished from impairment of consciousness (Blair, 2012).

2.3.2. Functional Neuroanatomy of Consciousness

Beginning in the 1930s through the 1950s, studies by Wilder Penfield and Herbert Jasper suggested that not only cortical structures are involved in the modulation of loss of consciousness, but subcortical structures (amygdala and hippocampus) are necessary (Mann & Cavanna, 2011; Yu et al., 2015). Penfield and Jasper denominate this complex interaction between networks of cortical and subcortical structures it the "*Centrencephalic Theory*" (Jasper, 1964; Penfield, 1958) and Blumenfeld (2008, 2012) called it the consciousness system.

The neuroimaging technologies in and physiological studies of human patients and animal models converge; despite the differences in symptoms and characteristics, generalized motor and nonmotor seizures and focal impaired awareness with motor or non-motor onset seizures have the same anatomical cortical and subcortical network involved in impaired consciousness. The cortical components include the medial frontal, anterior cingulate, posterior cingulate, and medial parietal (precuneus and retrosplenial) cortices on the medial surface, and the lateral frontal, orbital frontal, and lateral temporoparietal association cortices on the lateral surface. The

insula can be also involved. Subcortical components are basal forebrain, hypothalamus, thalamus, upper-brainstem, and segments of the basal ganglia, cerebellum, and amygdala (Bagshaw & Cavanna, 2011; Blumenfeld, 2005, 2012; Di Perri et al., 2014).

2.3.3. Levels of Consciousness in Epilepsy

Although awareness is important for the classification of epilepsy, the levels of consciousness during and after an epileptic seizure have not been investigated in much detail. To understand the levels of consciousness is important for knowing the cognitive abilities that the patient has after the seizure and for being able to determine whether a person is capable of continuing to perform the activity that was doing immediately before the epileptic seizure. As describe in the classification of epilepsy and epileptic seizures, Lüders et al. (2014) classified the loss of consciousness as dialeptic seizures, patient is not able to respond to external stimuli and this impairment can be partial or total.

For the ILAE classification three types of epileptic seizures cause impairment of consciousness: generalized nonmotor (absence), generalized motor and focal seizure with motor or non-motor onset. Generalized motor tonic-clonic seizures usually last 1-2 minutes with profound unresponsiveness to all external stimuli that continues into the postictal state and transiently resemble comatose patients, with the difference that the eyes typically remain open. During generalized nonmotor (absence) and focal to bilateral tonic-clonic seizures eyes remain opened and respond to external stimuli varies from no response to impaired or abnormal simple response, comparable to response in transient vegetative or minimally conscious state. In generalized non-motor seizures (absence) consciousness is lost for a brief period and tasks are interrupted; only simple repetitive actions can be continued during seizure. Consciousness returns rapidly, without any impairment and postictal state. Impaired responsiveness and awareness in focal seizures could be related to the duration of the recharge and seizure´s spread to contralateral cortical structures which continues during postictal state (Berman et al., 2010; Gloor et al., 1980; Inoue & Mihara, 1998; McPherson et al., 2012; Plum & Posner, 2007).

2.3.4. Evaluation of Consciousness during an Epileptic Seizure

Behavioral evaluation during and after epileptic seizures helps to determine an individual´s profile of cognitive strengths and weakness, levels of consciousness and language lateralization. Within epilepsy monitoring units, testing is used for presurgical evaluation, accurate diagnosis,

semiology, and evaluation of cognitive deficits; and aids in differentiating epileptic versus non-epileptic seizures (Touloumes et al., 2016).

Despite the fact that US-American National Association of Epilepsy Centers (Labiner et al., 2010) describe the importance of the application of a protocol for ictal assessment in the Guidelines for the Essential Services, Personnel, and Facilities in a Specialized Epilepsy Centers, a standardized behavioral testing protocol had not been created. Nonetheless, there is some agreement regarding the clinical features that should be included in such a testing protocol (Barry & Teixeira, 1983; Cavanna et al., 2008; Labiner et al., 2010; Nani & Cavanna, 2014; Noachtar & Peters, 2009; Perkins & Buchhalter, 2006):

1. level of consciousness or responsiveness
2. language
3. motor manifestation
4. memory
5. postictal behavior

In an effort to standardize behavioral testing, Touloumes et al. (2016) created a computerized Automatic Responsiveness Testing in Epilepsy (ARTiE) to detect seizures and consistently evaluate behavior. This software is in the development phase. Other protocols for evaluation of conscious states include Consciousness Seizure Scale (CSS), Ictal Consciousness Inventory (ICI), Prospective Responsiveness Scale (RES) and Seizure Perception Survey (SPS).

Recently, the ILAE published a recommendation on ictal testing in EMUs (Beniczky et al., 2016) At the Epilepsy Monitoring Unit of the University Hospital Ludwig-Maximilian in Munich a standard testing protocol which is common to all epilepsy surgery centers was used (see Methodology).

2.4. Postictal State

2.4.1. Definition of Postictal State

Finding an operational definition of the postictal state is complex because some unsolved problems have to be considered. Fisher & Engel (2010) identify five issues:

1. Determining the exact end of the ictus state is difficult. While some epileptic seizures have a behaviorally and electrographically well-demarcated end, most of the cases the end of the ictal state and the begin of the postictal state is not clear because ictal symptoms can continue postictally.
2. Many patients are unaware that they are having or had a seizure.
3. Cognitive, emotional and behavioral disability persists into the postictal state.
4. Postictal disturbances vary and it is difficult to determine when they are resolved as some patients are not aware of them.

For the purpose of this study the postictal state will be defined as a transient presence of electrophysiological and/or clinical abnormalities (in behavior, motor function, cognitive performance and mood changes) that appears after the ictal period until the return to a presumed baseline (Blume et al., 2001; Rémi & Noachtar, 2010).

2.4.2. Impairment of Consciousness in the Postictal State

Winesett et al. (2010) reported that the type of seizure, as well as locus of impact within the brain, affects the duration until complete recovery of consciousness is archived and what occurs before consciousness is recovered. Helmstaedter et al. (1994) determined that patients with focal impaired awareness seizure need from 1 to 10 minutes (Standard Deviation 3 minutes) for reorientation, while patients with generalized seizures require 4 to 45 minutes (SD 15 minutes). Some patients need more time to reorient because of postictal drowsiness, confusion, or sleep-state. Furthermore, patients declare persistent mental incapability even days after recovery from a seizure. Reorientation and the measuring of the time was not clearly explained in this study. Rehulka et al. (2014) noted that postictal unresponsiveness was five minutes longer in patients with bitemporal lobe epilepsy (75%) than in the group with temporal lobe epilepsy (30%).

2.4.3. Postictal State Semiology

People with epilepsy complain about the consequences of the epileptic seizure that are experienced during the postictal state like altered states of consciousness, fatigue, muscle pain, headache, aphasia, cognitive limitations, behavior and mood changes, mental incapability even days after the seizure, and general weakness or weakness in one part or side of the body (Blair, 2012; Fisher & Engel, 2010; Schmidt & Noachtar, 2010). The aim of this study is to analyze the influence of the level of consciousness, the cognitive deficits, the autonomic signs, and the

motor manifestations in the process of recovering consciousness during the postictal state, therefore only these will be mentioned.

2.4.3.1. Sleep and Postictal State

Sleep and epilepsy have a complex interaction, epilepsy disturbs sleep and sleep deprivation can trigger an epileptic seizure or aggravates epilepsy (Lanigar & Bandyopadhyay, 2014). Frontal lobe seizures begin more frequently during sleep, and temporal lobe seizures are more likely to secondary generalized during sleep (Bazil, 2010; Crespel et al., 1998; Hermann et al., 1997; Provini et al., 1999; Yaqub et al., 1997).

When seizures occur during sleep, as in non-motor generalized epilepsy, myoclonic epilepsy, generalized tonic-clonic epilepsy, benign rolandic epilepsy, Landau-Kleffner syndrome and electrical status epilepticus; or occurs between sleep and wakefulness, as in juvenile myoclonic epilepsy, patients are often unaware, as patients have a brief awakening and the postictal state could be confused with normal sleep. Postictal signs and symptoms like confusion, drowsiness, incontinence, sleep walking, sleep talking, attention problems and memory dysfunction can be mistaken with sleep disorders (Bazil, 2010; Lanigar & Bandyopadhyay, 2014).

2.4.3.2. Postictal Cognitive Deficits

Patients with epilepsy complain of cognitive deficits during postictal state such as impaired ability to remember new material or recall previously remembered material; decreased cognitive performance involving perception, execution, praxis, attention, language; and difficulties in performing daily activities. Cognitive changes are more significant immediately after the seizure (Aldenkamp et al., 1992, 1996). Effects of postictal cognitive impairment have been less studied; further investigation is needed to better understand these deficits.

2.4.3.2.1. Language Manifestation

Studies have demonstrated the high value of postictal verbal manifestations as a lateralization sign if present in more than one seizure. Standard protocols for testing postictal language include evaluating dysphasia and aphasia, and confrontation-naming. Speech manifestation could be overshadowed by altered level of consciousness and by other features of seizures that gain more attention due to their more established lateralizing value (Gabr et al., 1989; Privitera

et al., 1991; Ramirez et al., 2008). Privitera et al. (1991) held that postictal confusion in patients with temporal lobe epilepsy with focal to bilateral seizures could be confused with a transient disruption of receptive or expressive language abilities; it is crucial to clinically differentiate postictal confusion and aphasia by testing language and speech during the postictal state.

Physicians often consider aphasia as a sign of lateralization to the dominant hemisphere in patients with temporal lobe epilepsy with focal to bilateral tonic-clonic seizure, with predictive value between 80% and 100% (Fakhoury et al., 1994; Gabr et al., 1989; Leutmezer et al., 2002; Noachtar & Peters, 2009). Adam et al. (2000) and Koerner & Laxer (1988) observed that patients with dominant hemisphere onset had postictal aphasia and patients with non-dominant hemisphere onset and with extratemporal seizures did not present postictal language impairment. In that cases aphasia only appears, if the seizure propagates to the dominant temporal lobe (Ficker et al., 2001; Ramirez et al., 2008). Salanova et al. (1992) noted postictal aphasia in 7.3% and 10.9% of the patients with occipital epilepsy. Aphasia is more pronounced in patients with structural lesion (Goldberg-Stern et al., 2005).

In their study, Koerner and Laxer (1988) and Gabr et al. (1989) determined that dysphasia has an important value in differentiating dominant and non-dominant hemisphere in 92% of the patients with temporal lobe epilepsy. Privitera et al. (1991) also detected phonemic paraphasia (incorrect phoneme or morpheme substitution) while patients read the test phrase in 74% (46/62 seizures) of left temporal lobe epilepsies and 0% (0/43 seizures) of right temporal lobe epilepsies.

Studies suggest that postictal language delay accurately predicts the dominant hemisphere (Fargo et al., 2005; Ramirez et al., 2008; Schefft et al., 2003). Privitera et al. (1991) measured the time-lapsed between the end of the EEG ictal discharge and the moment when a patient read a test phrase correctly in 126 patients. They reported that patients with left temporal lobe epilepsy take more than 60 seconds to correctly read the test phrase than patients with right temporal lobe epilepsy. With this simple assessment seizure onset classification can be done in less than 2 minutes.

Studies have reported impaired performance in confrontation naming (ability to apply semantically and phonemically correct labels or names to visually presented stimuli) in patients with temporal lobe epilepsy, which worsens if the dominant hemisphere is involved (Busch et al., 2005; Fargo et al., 2005; Schefft et al., 2003).

2.4.3.2.2. Postictal Memory Deficits

Patients with temporal lobe epilepsy complain about memory loss. Studies found that perceived verbal memory and learning deficits are the consequences of a mild language impairment and less of memory impairment (Hermann et al., 1997; Mayeux et al., 1980; Ramirez et al., 2008). Helmstaedter et al. (1994) studied postictal cognitive deficits in right and left temporal lobe, and frontal lobe patients to clarify the degree and duration of postictal deficits complaints. According to their findings, postictal verbal memory is significantly decreased in left temporal lobe epilepsy compared to right temporal lobe epilepsy, and visuospatial memory is more impaired in right temporal lobe epilepsy in comparison with left temporal lobe epilepsy. Frontal lobe patients did not have changes in verbal and spatial orientation memory. Verbal and non-verbal memory testing in postictal phase has a lateralization value. These outcomes are in concordance with other studies findings (Andrewes et al., 1990; Delaney et al., 1980; Pegna et al., 1998; Vannucci, 2007; Vulliemoz et al., 2012).

Patients with epilepsy can be unaware of occurrence, timing, and semiology of their seizure, they do not report 26-50% of their seizures. Investigations point out a higher proportion of unreported seizures when seizures rise from the left hemisphere. Alteration of memory and level of consciousness are associated to this hemisphere. Another important factor for seizure report is the patient´s state of vigilance at the time of the seizure. Furthermore, memory may be disrupted before and after nocturnal seizures, though the relationship of memory dysfunction in underreporting of seizures has still not investigated. Further work is needed to develop a complete understanding of the factors that influence seizure report, including seizure localization, preictal vigilance state, levels of consciousness during and after the seizure, memory function and seizure type (Englot et al., 2010; Hoppe et al., 2007; Janszky et al., 2004; Kerling et al., 2006; Tatum et al., 2001).

2.4.3.3. Postictal Motor Manifestations

Automatisms are the postictal motor manifestation analyzed in this study. These are known as automatic complex movement that are repeated redundantly. Ictal and postictal automatisms, such as smacking, chewing, and finger rubbing, are distinguishable only with video-EEG monitoring, though movement parameters have not been established yet (Rémi & Noachtar, 2010). For Baykan et al. (2011) automatisms occurred similarly in focal and generalized epilepsies; however, Henkel et al. (2002) consider automatisms as a prominent sign of focal

epileptic seizures. Inoue & Mihara (1998) establish that patients with automatic behavior do not recall events during their seizure.

2.4.3.4. Postictal Autonomic Signs

Nose-rubbing, coughing, spitting and heart beating have been reported so far as postictal vegetative lateralization signs in focal epilepsies (Fauser et al., 2004; Hoffmann et al., 2009). Nose-rubbing immediately after the seizure has a predictive value of 90% to 97% in patients with temporal lobe epilepsy. This sign is particularly predictive of mesial temporal lobe epilepsy as compared with extratemporal lobe epilepsy. The hand used to perform postictal nose wiping is ipsilateral to the side of seizure´s origin due to contralateral neglect or weakness (Geyer et al., 1999; Hirsch et al., 1998; Leutmezer et al., 1998). Postictal nose-rubbing did not occur after secondarily generalized seizures, generalized epilepsy, or non-epileptic seizures (Geyer et al., 1999). Hirsch et al. (1998) hypothesize ictal nasal secretions causes nose wiping as the patient regains awareness in the postictal state.

Postictal coughing occurs in response to increased respiratory secretions and activation of central autonomic networks and it mainly occurs in focal to bilateral tonic-clonic seizures (Bogolioubov et al., 1994; Gil-Nagel et al., 1997; Stefan et al., 2001; Van Ness et al., 1993; Wennberg, 2001). In temporal lobe epilepsy, coughing is a regular element of seizure semiology indicating non-dominant epileptic focus, in extratemporal lobe epilepsy it appears only sporadically (Gil-Nagel et al., 1997; Wennberg, 2001). Fauser et al. (2004) hold that the occurrence of occasional coughing cannot be used to differentiate temporal and extratemporal lobe epilepsy. Incidence of postictal coughing in patients with temporal lobe epilepsy is predictively 9 – 40% of times with a right-sided lateralization and mesial temporal localization, but is not statistically significant (Bogolioubov et al., 1994; Gil-Nagel et al., 1997; Van Ness et al., 1993). For Fauser et al. (2004) coughing is related to the left temporal lobe. Because of contradictory results in the mentioned studies, coughing remains of doubtful lateralizing value.

Chapter 3. Methodology

3.1. Research Design

In order to investigate the duration that a person with temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE) needs to give a first adequate response (FAR) during the postictal state and identify the factors that affect the time to recover consciousness, a quantitative research design was chosen using a descriptive and a correlational approach. The descriptive method is useful when not much has been investigated about a topic, it allows to observe and explain the phenomenon in a completely natural and unchanged environment, and helps to identify characteristics, frequencies, correlations, patterns, trends, and categories. Observations allow to gather data on behaviors, signs and symptoms, and to describe them systematically. This research design attempts to collect quantifiable information to be used for statistical analysis (Adams et al., 2007; Dulock, 1993; Giorgi & Giorgi, 2003).

3.2. Ethics Committee and Data Protection

Data collection was done according to the "Proposed International Guidelines for Biomedical Research Involving Human Subjects" (The Council for International Organizations of Medical Sciences, 2002) and this doctoral thesis complies with the recommendations of the medical faculty for the analysis of anonymized patient-data, all identifiable data remained in the clinical data systems. The patients gave written informed consent to the scientific use of their data and the ethics committee of the LMU approved the retrospective scientific use of these clinically acquired data.

3.3. Sources of Data

The entire work was performed at the Epilepsy Monitoring Unit (EMU) at the Hospital of the Ludwig Maximilians University of Munich. Patients were referred by the treating neurologist to the EMU for a complete presurgical epilepsy diagnostic workup for possible epilepsy surgery according to standardized protocols, to verify the diagnosis, to change medication or for a differential diagnosis evaluation (Noachtar et al., 1998). For this purpose, patients were hospitalized to be monitored for at least three days. Scalp surface EEG-electrodes were placed using the international 10 – 20 system (American Electroencephalographic Society 1991) with

additional 10-10 electrodes if needed. 40 channel EEG machines (XLTEK, Ontario, Canada) were used. All patients with temporal lobe epilepsy received sphenoidal electrodes on both sides, due to their positioning near the foramen oval (Wilkus & Thompson, 1985). Electrodes recordings were obtained and visualized using a standard clinical system (XLTEK, Ontario, Canada) at a sampling rate of 512 Hz for scalp video-EEG.

Patients were monitored by technical assistants 24 hours per day during their stay in the monitoring unit. When a seizure occurred, technical assistants secured the patients physical well-being and started cognitive and behavioral evaluation until they considered consciousness was recovered. The cognitive and behavioral assessment used in the EMU at the LMU is as follow:

1. Test word (x1): ask to remember a simple word (like "car", "book", "sun")
2. Give me your first Name
3. Lift your arms
4. Test objects: show!
    - What is this?
    - What is it used for?

If patient is aphasic, it is important he/she shows the use of the objects, so one knows he/she understands the question, but cannot name the object.

5. When the patient is thought to have recovered consciousness and responds to first questions, further details are asked:
    - Do you remember the test word?
    - When did you have your last seizure?
    - How do you feel now?

Once the patients regained consciousness, EMU staff used a structured interview to determine whether they recalled having an aura and/or a seizure, have had postictal aphasia, or had any recall of what happened during the seizure (Baykan et al., 2011).

The video-EEG was analyzed from an electroclinical perspective for the classification of the seizure. In addition to the EEG analysis, the video recording was used to document signs of lateralization, symptoms, states of consciousness, aphasia and whether the patients were able to respond to the cognitive and behavioral evaluation during the seizure.

The classification was based on localizing findings of Video-EEG-Monitoring and diagnostic imaging. The imaging epilepsy diagnostic of all patients in this study included MRI and, in many cases, FDG-PET and ictal ECD-SPECT. Information from at least two of these methods were required for localization of the seizure onset zone and further spreading to other brain regions. A senior epileptologist classified the seizures according to Lüders Semiological Seizure Classification (Lüders et al., 1998; Noachtar et al., 1998), classification used in the EMU of the Hospital of the LMU.

3.4. Selection of the Study Population

The present work is a retrospective case series analysis of clinical data from patients of the EMU at the Hospital of the LMU examined and treated in the period from March 2006 to December 2018. For the patient population selection two phases were established: the first was focused on the medical records to identify patients diagnosed only with temporal and frontal lobe epilepsy and the second phase on the description and analysis of the video-EEG.

Phase I: Selection of Patients

For the identification of the patient population medical reports were reviewed to enlist patient with the following requirements:

1. Established diagnosis of temporal and frontal lobe epilepsy with clear hemispheric lateralization.

2. Patients had to be over 8 years because of reported effect of age on the seizure semiology (Fogarasi et al, 2002),

3. At least one video-EEG-documented seizure had been recorded.

Phase II: Selection of Epileptic Seizure

Patient reports were reviewed to select epileptic seizures for analysis. Seizures and the video-EEG data had to meet the following conditions to be included in this study:

1. The seizure remained "focal", i.e. it did not evolve into a secondarily generalized tonic-clonic-seizure.

2. The seizure did not evolve into a status epilepticus.

3. Videos with good resolution where patients' body and face were visible.

4. Consciousness was regained during the postictal state.

5. Adequate ictal and postictal testing of consciousness.

6. Clear end of ictal pattern.

Videos-EEG exclusion criteria:

1. Patients who did not understand the ictal and postictal testing because of language barrier or cognitive limitations.

2. Patients that recovered consciousness before ending the ictal state were excluded as the aim is to determine the time that patients with epilepsy need to recover consciousness during the postictal state.

The videos were anonymized and the retrieved analysis data was stored in an anonymized spreadsheet. All videos remained in the clinical systems.

3.5. Data Gathering Procedure

Once the patients and the epileptic seizures to be analyzed were identified, the factors were collected as follows:

3.5.1. Clinical Data

From the medical history clinical data was extracted. Numerical values were assigned to nominal variables for statistical analysis.

3.5.1.1. Epilepsy and Epileptic Seizures Type

The categorization of the epilepsy and epileptic seizures was based on the ictal semiology from Lüders et al. (1998), classification used in the EMU of the LMU. For each patient, a maximum of 11 seizures were analyzed. Some patients had more seizures, but this arbitrary cut off was chosen to not skew the results towards the results from single patients with extensively more seizures. For the final analysis of seizure duration, the median duration was taken.

3.5.1.2. Age at Admission to the EMU

The age at the first day of admission was documented.

3.5.1.3. Sex

The percentage of female [=0] and male [=1] was analyzed.

3.5.1.4. Laterality

Laterality was distributed in right-handed [=0], left-handed [=1] and ambidextrous [=2].

3.5.1.5. Age at Epilepsy Onset

Age of the first epileptic seizure was documented.

3.5.1.6. Duration of Epilepsy

Years that the person has had epilepsy were considered from the day of diagnosis to the first day of admission to the EMU.

3.5.2. Video-EEG Data

The video-EEGs were carefully analyzed to obtain the variables that were used in this study. For nominal variables numerical values were assigned for statistical analysis.

3.5.2.1. Time Recovering Consciousness

The aim of this research is to determine the time patients need to recover consciousness (RC) during the postictal state. This time ranges from the end of the ictal state to the first adequate response (FAR) in the postictal state. The FAR is considered when the patient reacts correctly to two consecutive instructions given by the technical assistants, such as: saying the name, following instructions (e.g.: "lift the arms"), naming the object that is presented or showing for what that object can be used (if patient is aphasic). Postictal aphasia may impair spoken responses by the patients and even understanding verbal instructions. Therefore, the typical testing regimen also includes non-verbal commands and cues, namely performing the requested task as an example by the technician. The time of the first correct response was documented. The FAR was taken in this research as the first sign of recovering consciousness.

In this project the patients' ability to give two consecutive correct answers is taken as a crucial sign of recovery of consciousness. This means the patient is no longer confused, is aware of his/her surroundings and capable to react correctly to the instructions, but this does not exclude that the patient may be tired and need to sleep to regain strength. Analyzing when the patient is at his/her full capacity to resume the activities, he/her was performing before the seizure and does no longer present postictal symptoms such as memory and attention difficulties, as well as emotional disorders is beyond the extent of this study.

3.5.2.2. Amount of Seizures on the Same Day before the analyzed Seizure

All seizures before the analyzed seizure between 12:00 midnight to 11:59 p.m. on the same day.

3.5.2.3. State of Consciousness before Seizure

The patient´s state of consciousness before seizure onset was documented as awake [=0] and sleeping [=1].

3.5.2.4. Duration of the Seizure

Since it is difficult to determine when the ictal state ends and the postictal state begins, for the purpose of this study the ictal state was established with the EEG according to the onset and

end of the EEG seizure pattern. Seizure time is the EEG seizure pattern duration. The postictal state begins with the end of the EEG seizure pattern.

3.5.2.5. Level of Consciousness after Seizure

Impairment of consciousness was defined as an inadequate or missing response to the stimuli during cognitive and behavioral testing done by EMU staff. The levels of consciousness were classified according to the ILAE definition of responsiveness (Plum & Posner, 2007):

Table 4. Definition of Level of Consciousness

Level of consciousness	Definition
Normal	able to respond promptly and spontaneously to name, location and date/time
Confused	does not respond quickly, is disoriented and has difficulties following instructions
Delirious	disoriented, hallucinations/delusions, restlessness
Drowsiness	somnolent, sleepy
Obtunded	slowed psychomotor responses and decreased interest in their surrounding
Stuporous	no spontaneous activity, respond by grimacing or drawing away from painful stimuli
Comatose	no response to stimuli, no pupillary response

Numerical values were assigned to the different consciousness levels for statistical purpose: normal [=0], confused [=1], delirious [=2], drowsiness [=3], obtunded [=4], stuporous [=5], comatose [=6].

3.5.2.6. Ictal and Postictal Semiology

To explore the recovery process of consciousness in the postictal state and the kind of factors that influence the impairment of consciousness, ictal and postictal semiology were described as it appeared: manual an oral automatisms, smacking, laughing, coughing, nose rubbing, vocalization, gape, gaze, vocal automatisms and hiccup.

3.5.2.7. Postictal Aphasia

When studying the recovery of consciousness, adequate reactions by the patient are key to recognize recovery of consciousness. Postictal aphasia can be present in epilepsy, especially in left hemispheric epilepsy. This could be a potential bias, when only aphasic patients would be found to regain consciousness later. Therefore, postictal aphasia had to be evaluated.

The type of aphasia studied was anomic aphasia, which is an inability of naming a test object but demonstrating other forms of language understanding, for example following commands. The duration of anomic aphasia was documented from the end of the seizure until the patient was able to name the test objects during the postictal state.

The ability or inability of naming objects may not be completely consistent in a single patient but may rather fluctuate in the postictal state. Therefore, in this research, partial dysnomia was also noted and considered as the capacity of patients to name two or three objects but having difficulty to name the next one to three objects, alternately naming objects and difficulty to name them.

3.6. Statistical Analysis

The collected data was analyzed through PASW Statistics version 18 for descriptive analysis, significance test, linear regression and figures. For categorical variables such as sex, laterality, state of consciousness before seizure and level of consciousness after seizure percentages was determined. For continuous data mean, standard deviation, median, maximum and minimum were calculated.

The data of this study is non-parametric therefore, the Mann Whitney U Test was used to compare the outcomes between two independent groups when the dependent variable was ordinal or continuous and Wilcoxon Test to compare two paired groups. To measure the degree of association between two continuous variables Pearson correlation coefficient was used and to assess significant differences on a continuous dependent variable and a categorial variable in three or more groups Kruskal-Wallis Test. Linear Regression Analysis was used to investigate the influence of one or more independent variables on a dependent variable, to determine the extent of a linear relationship between the independent variables and the dependent variable. Statistical significance was considered at $p < 0.05$. Multiple Testing was corrected by the

Bonferroni-Holm-correction, when applicable. Also, unnecessary testing for small group sizes was avoided.

3.7. Research Hypotheses

The hypotheses of this investigation are:

The first hypothesis is based on the relation between the four groups and the time to regain consciousness:

> H_0: the duration to regain consciousness (RC) is similar in persons with right temporal lobe epilepsy (RTLE), left temporal lobe epilepsy (LTLE), right frontal lobe epilepsy (RFLE) and left frontal lobe epilepsy (LFLE).
>
> H_1: the duration to RC is different in persons with RTLE, LTLE, RFLE and LFLE.

The second hypothesis is based on if the clinical characteristics of the patients influence in the time to regain consciousness:

> H_0: the duration to give an adequate response during the postictal state is independent of the clinical characteristics of the person with RTLE, LTLE, RFLE and LFLE.
>
> H_1: the clinical characteristics of the person with epilepsy influences the duration to RC in patients with RTLE, LTLE, RFLE and LFLE.

The third hypothesis is based on the relation between the characteristics of the epileptic seizure and the time to regain consciousness:

> H_0: the characteristics of the epileptic seizures have no influence in the duration to RC during the postictal state in patients with RTLE, LTLE, RFLE and LFLE.
>
> H_1: the characteristics of the epileptic seizure influence the duration to RC during the postictal state in patients with RTLE, LTLE, RFLE and LFLE.

Chapter 4. Results

Based on the assumption that impaired consciousness during the postictal state has consequences for safety, productivity, emotional health, cognitive functioning and quality of life (Blumenfeld, 2012), the aim of this study was to investigate the duration to give the first adequate response (FAR) during the postictal state (taken as the first sign of the recovery of consciousness), and the factors that can influence the length of time. In this investigation regaining consciousness (RC) was considered when the patient gave the FAR to the cognitive and behavioral evaluation done by the staff of the Epilepsy Monitoring Unit (EMU).

In this retrospective study information was collected from the data base of the EMU at the LMU, examined and treated in the period from March 2006 to December 2018. The first step was to review medical history to select patients over eight years of age, diagnosed with TLE and FLE by a senior epileptologist, had clear hemisphere lateralization, and at least one documented seizure video-EEG. As a second step technically good video-EEGs with adequate ictal and postictal testing of consciousness and where the patient body and face were visible were selected and analyzed. For each patient, a maximum of 11 seizures were analyzed. For the final analysis of the seizure median duration was taken.

Patients were divided in four groups according to the diagnosis: RTLE, LTLE, RFLE and LFLE. The analyzed factors were divided into two groups: clinical features and the characteristic of epileptic seizures. The clinical characteristics were sex, age at admission to the EMU, age at epilepsy onset, duration of epilepsy and laterality. The characteristics of the epileptic seizures were location, seizure type, amount of seizures on the same day before the analyzed epileptic seizure, level of consciousness before the seizure, level of consciousness after the seizure, duration of the seizure (duration of epileptic seizure pattern), ictal and postictal semiology, postictal coughing and postictal aphasia.

4.1. Characteristics of the Participants

4.1.1. Time Recovering Consciousness during the Postictal State

In general, patients needed 81.7 ± 80.4 seconds to give the FAR, with a median time of 52 seconds, and a range from 5 to 342 seconds. At the EMU Lorazepam 2 mg was given to patients

with three seizures in a single day or with a generalized seizure as a seizure rescue medication to prevent status epilepticus. In this study Lorazepam was given to 16 patients (8.51%) after the FAR, only two intakes of the medication were seen on the video.

4.1.2. Clinical Characteristics

A total of 332 seizure videos of 188 patients were selected for this study. The average age was 39.8 ± 14.5 years. The oldest patient was 77 and the youngest 13 years old, with a median age of 40.5 years. Ninety-seven were female (51.6%) and 91 male (48.4%). Laterality was distributed in 149 right-handed (79.3%), 20 left-handed (10.6%) and 19 ambidextrous (10.1%).

The first epileptic seizure of the patients appeared in a range from 9 month to 72 years of life with a median of 13 years (mean 16.5 ± 14.7 years) and with an evolution of 23.5 ± 16.8 years (range, 4 month to 73 years, median 22 years).

4.1.3. Characteristics of Epileptic Seizures

Sixty-nine patients (36.7%) had no seizures on the same day as the analyzed epileptic seizure, 59 patients (31.4%) had one seizure, 27 patients (14.4%) two seizures, 18 patients (9.6%) three seizures, seven patients (3.7%) four seizures, three patients (1,6%) five seizures, two patients (1.1%) six seizures, two patients (1.1%) seven seizures and one patient (0.5%) 11 seizures.

Prior to the epileptic seizure 106 patients were awake (56.4%) and 82 sleeping (43.6%). Mean seizure duration was 69.3 ± 42.7 second (range, 14 to 279 seconds; median 60 seconds). During the ictal state 68 patients (36%) had only one sign, 26 patients (8.5%) two signs, 20 patients (10.6%) had three, seven patients (3.7%) four, three patients (1.6%) five, and one patient (0.5%) seven. After the seizure 144 patients were confused (76.6%), 18 felt sleepy (9.6%), 22 obtunded (11.7%), one stuporous (0.5%) and three were comatose (1.6%).

During the postictal state 43 patients (22.9%) presented one postictal sign, 29 patients (15.4%) two signs and symptom, 16 patients (8.6%) three, six patients (3.2%) four, two patients (1.1%) five, two patients (1.1%) seven, and one patient (0.5%) eight. Fourteen patients (7.4%) had one cough before given the FAR, seven patients (3.7%) had two coughs, three patients (1.6%) three coughs, and in one patient (0.5%) four coughs. Language disorders were divided in thirty-one patients (16.5%) with postictal anomia, nineteen patients (10.1%) with partial dysnomia, four

patients (2.1%) with anomia and partial dysnomia, 14 patients (7.4%) spoke incomprehensible, and two patients (1.1%) responded with numbers to the questions done by the staff of the EMU.

4.2. Characteristics of the Participants according to the Epileptic Seizure onset

4.2.1. Clinical characteristics

4.2.1.1. Epilepsy diagnosis

The studied population consisted of 188 patients: 66 patients with RTLE, 85 patients with LTLE, 18 patients with RFLE, and 19 patients with LFLE. All study subjects were inpatients of the Epilepsy Monitoring Unit (EMU) at the Ludwig Maximilian University Hospital in Munich who were examined and treated in the period from March 2006 to December 2018 (Table 5).

Table 5. Number of patients and epileptic seizures according to diagnosis

	Patients			*Epileptic Seizures*		
Lobe	N	Hemisphere		N	Hemisphere	
		Right	Left		Right	Left
Temporal	**151** (80.3%)	66 (43.7%)	85 (56.3%)	**251** (75.6%)	114 (45.4%)	137 (54.6%)
Frontal	**37** (19.7%)	18 (48.7%)	19 (51.4%)	**81** (24.6%)	46 (56.8%)	35 (43.2%)
Total	**188**	84	104	**332**	160	172

4.2.1.2. Epileptic Seizure Type

Automotor seizures occurred in all four groups (LTLE, n = 31; RTLE, n = 32; RFLE, n = 4; LFLE, n = 3). Complex-motor seizures were diagnosed in three groups: RFLE (n = 3), LTLE (n =8) and RTLE (n =7). Three patients had a complex-motor seizure that evolved to one or two other seizure types in the LFLE group. Only temporal lobe patients were diagnosed with aura + automotor seizures (RTLE, n = 15; LTLE, n =13). This type of seizure develops into a versive seizure in one patient with RTLE and another with LTLE, and to a complex-motor seizure in one patient with RTLE and one with LTLE. On the other hand, only frontal lobe patients presented hypermotor seizures (LFLE, n =3; RFLE, n = 1).

Dialeptic seizures were present in all four groups: 13 patients in the LTLE group, four patients in the RTLE group, one patient in the RFLE and one patient in the LFLE group. Furthermore, in the

RTLE group one patient had a dialeptic seizure -> automotor seizure, and one patient with aura -> dialeptic seizure -> tonic seizure. Three patients of the LTLE group (n = 3) were diagnosed with dialeptic seizure -> automotor seizure. One patient in the LFLE group had a dialeptic seizure -> aphasic seizure, and one patient of the RFLE group had a dialeptic seizure + automotor seizure.

Other seizure types that were less common were aphasic seizures (LTLE, n = 2), aura -> aphasic seizure (LTLE, n = 2), tonic seizures -> hypermotor or complex-motor seizure (RFLE, n = 4), vegetative seizure -> automotor seizure (RTLE, n = 3) and aura -> versive left seizure -> automotor seizure (LTLE, n = 1) (Appendix A, B and C).

4.2.1.3. Age at Admission to the EMU

Patients with frontal lobe epilepsy were statistically significant younger at admission to the EMU than temporal lobe epilepsy patients ($p < 0.05$). Patients with LFLE had a median age of 27 years and patients with RFLE 31 years. Patients with LTLE had a median age of 44 years and patients with RTLE had a median age of 42 years. Furthermore, patients with left hemisphere were statistically significant older than patients with right hemisphere seizure onset ($p < 0.05$) (table 6).

Table 6. Age at Admission to the EMU

			Years				
Lobe	Hemisphere	N	Mean	SD	Median	Minimum	Maximum
Temporal	Right	66	38.3*	12.6	42	18	61
	Left	85	44.6*	14.7	44	19	77
Frontal	Right	18	34.5*	14.0	31	16	60
	Left	19	28.8*	12.3	27	13	56

*= $p < 0.05$ for frontal and temporal lobe, and right and left hemisphere

4.2.1.4. Sex

The percentage of woman was higher in TLE and males in FLE. Patients with RTLE were 37 females (56.1%) and 29 males (43.9%), and in patients with LTLE 49 were females (57.6%) and 36 males (42.4%). In RFLE males were 13 (72.2%) and females 5 (27.8%), and in LFLE 13 were males (68.4%) and 6 females (31.6%).

4.2.1.5. Laterality

In all four groups right laterality prevailed, while the number of patients with left and ambidextrous laterality were similar (table 7).

Table 7. Laterality according to localization

		Localization				
		N	*Temporal*		*Frontal*	
			Right	Left	Right	Left
Laterality	Right	149 (79.3%)	49 (74.2%)	72 (84.7%)	13 (72.2%)	15 (78.9%)
	Left	20 (10.6%)	9 (13.6%)	6 (7.1%)	2 (11.1%)	3 (15.8%)
	Ambidextrous	19 (10.1%)	8 (12.1%)	7 (8.2%)	3 (16.7%)	1 (5.3%)

4.2.1.6. Age at Epilepsy Onset

Patients with FLE were statistically significant younger when they had their first epileptic seizure in relation to patients with TLE ($p < 0.01$). Patients with LFLE had their first epileptic seizure at a mean age of 7.8 ± 6.5 years, patients with RFLE 11.7 ± 12.2 years, with RTLE 17.7 ± 14.7 years and with LTLE 18.5 ± 15.7 years.

Dividing the groups according to the age of onset in ranges from 0 to 9 years, 10 to 19 years and > 20 years, 79.0% of the patients with LFLE and 55.6% of the patients with RFLE had their first epileptic seizure between 0 – 9 years. The percentage of the patients with RTLE and with LTLE were almost equally divided in the three groups.

4.2.1.7. Duration of Epilepsy

Patients with left hemisphere seizure onset zone had a longer duration of epilepsy, 26 years for temporal lobe patients and 23 years for frontal lobe patients. On the other hand, patients with right hemisphere seizure onset zone had a duration of 18 years for frontal lobe patients and 15 years for temporal lobe patients (table 8).

Table 8. Duration of the Epilepsy

		Years					
Lobe	Hemisphere	N	Mean	SD	Median	Minimum	Maximum
Temporal	Right	66	20.8	16.7	15	0	54
	Left	85	26.1	17.8	26	1	73
Frontal	Right	18	22.8	13.9	18	6	50
	Left	19	21.1	13.6	23	1	49

4.2.2. Time to Recover Consciousness during the Postictal State

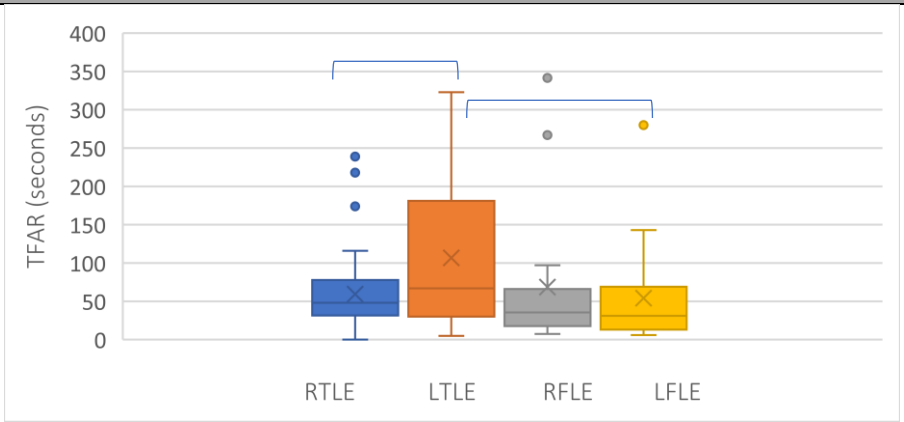
Patients with LTLE required statistically significantly more time to RC (mean 106.8 ± 93.7 seconds) in relation to RTLE (mean 60.9 ± 48.3 seconds) ($p < 0.05$) and LFLE (mean 54.2 ± 66.6 seconds) ($p < 0.01$) (table 9, figure 2).

Table 9. Time to Regain of Consciousness according to location of epilepsy

Lobe	Hemisphere	N	Mean	SD	Median	Minimum	Maximum
Temporal	Right	66	60.9*	48.3	49	7	239
	Left	85	106.8**	93.7	67	5	323
Frontal	Right	18	68.6	90.5	36	8	342
	Left	19	54.2**	66.6	31	6	280

*= $p < 0.05$ for LTLE vs RTLE
**= $p < 0.01$ for LTLE vs LFLE

Figure 2. Time to give a first adequate response (TFAR) according to Localization



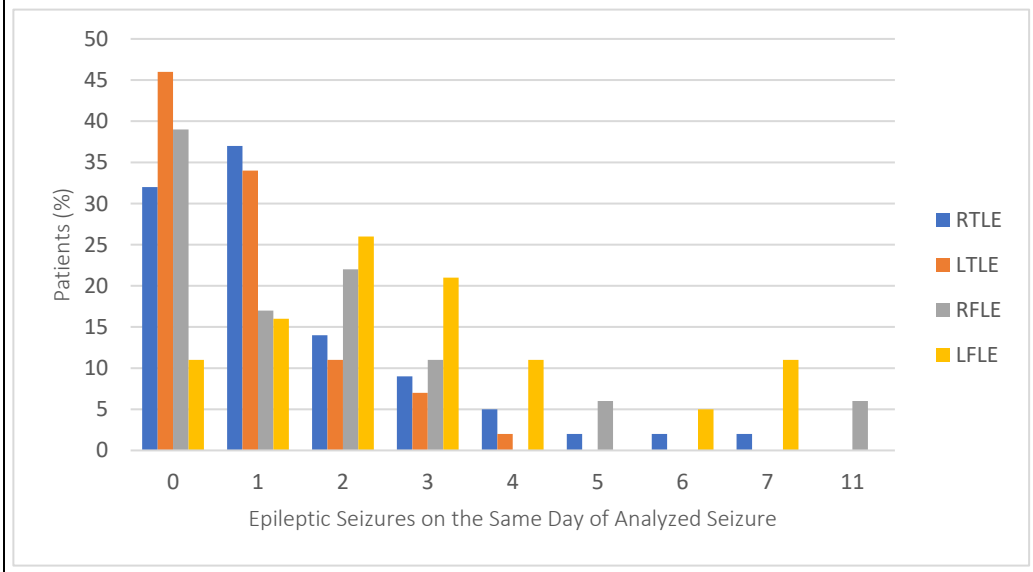
*= $p < 0.05$ for LTLE vs RTLE
**= $p < 0.01$ for LTLE vs LFLE

4.2.3. Epileptic Seizure Characteristics

4.2.3.1. Amount of Epileptic Seizures on the Same Day of the Analyzed Seizure

On the same day of the analyzed seizure patients with temporal lobe epilepsy had from no seizure to one seizure before, 31.8% of the patients with RTLE had no seizure and 36.4% one seizure, and in 45.9% of the patients with LTLE had no seizure and 34.1% one seizure. Patients with frontal lobe epilepsy presented no seizure or one or two seizures before the analyzed seizure. In 38.9% of the patients with RFLE had no seizures and 22.2% two seizures, and 26.3% of the patients with LFLE two seizures and 15.8% one seizure (figure 3).

Figure 3. Epileptic Seizures on the Same Day of the Analyzed Seizure



4.2.3.2. State of Consciousness before the Seizure

Temporal lobe patients were awake before the epileptic seizure in 59.1% of the right hemisphere cases and in 65.9% of the left hemisphere cases. On the other hand, RFLE were mostly sleeping (88.9%). The percentage of sleeping (52.6%) and awake (47.4%) patients in LFLE were almost the same.

4.2.3.3. Duration of the Seizure

The duration of the seizure ranged from 14 to 279 seconds. In the right hemisphere patients with temporal lobe epilepsy onset had a statistically significant longer duration of the seizure in relation to patients with frontal lobe epilepsy ($p < 0.01$). Furthermore, there was a statistically significant difference between the duration of the seizure in right hemisphere and left hemisphere lateralization ($p < 0.01$) (table 10).

Table 10. Duration of Seizure according to location

Lobe	Hemisphere	N	Mean	SD	Median	Minimum	Maximum
Temporal	Right	66	74.4**	47.2	63	14	279
	Left	85	70.5**	37.7	62	14	186
Frontal	Right	18	61.6**	39.4	50	20	178
	Left	19	53.6**	48.9	32	17	214

**= p < 0.01 for RTLE and RFLE, LTLE and LFLE

4.2.3.4. Ictal Motor and Autonomic Semiology

Discrete ictal signs and symptoms were more common in patients with TLE as compared to FLE, with manual automatisms ($p < 0.0001$) and oral automatisms ($p < 0.0001$) being statistically significant more frequent (table 11).

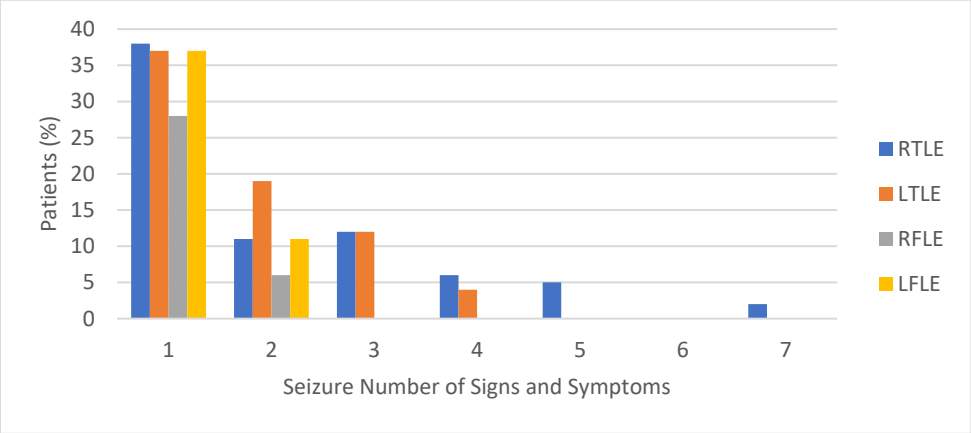
Table 11. Ictal Motor and Autonomic Semiology (IS)

Signs	Location							
	Temporal				*Frontal*			
	Right		*Left*		*Right*		*Left*	
	n (IS)	n (%)	n (IS)	n (%)	n (IS)	n (%)	n (IS)	n (%)
Manual Automatisms	49	74.2***	59	69.4***	4	22.2***	4	21.1***
Oral Automatisms	33	50.0***	32	37.6***	2	11.1***	2	10.5***
Smacking	5	7.6	4	4.7	0	0	0	0
Laughing	4	6.1	3	3.5	0	0	0	0
Coughs	2	3.0	1	1.2	0	0	1	5.3
Nose-rubbing	4	6.1	2	2.4	0	0	0	0
Vocalization	3	4.5	2	2.4	1	5.6	3	15.8
Gaze	1	1.5	1	1.2	0	0	0	0
Hiccup	0	0	0	0	0	0	1	5.3
Verbal automatisms	0	0	1	0	0	0	0	0

***= p < 0.0001 for RTLE and RFLE, LTLE and LFLE

Patients with temporal lobe epilepsy had from one to seven signs and symptoms during the seizure. Patients with frontal lobe epilepsy had only one or two signs and symptoms (figure 4).

Figure 4. Number of signs and symptoms during the seizure



4.2.3.5. Level of Consciousness after Seizure

In case conscious ness was quantitatively impaired, confusion was most common (RFLE 88.9%, LFLE 84%, LTLE 83.5%, RTLE 62.1%). Other levels of consciousness were obtunded (LFLE 15.8%, RTLE 13.6%, RFLE 11.1%, LTLE 9.4%), drowsiness (RTLE 18.2%, LTLE 7.1%), stuporous (RTLE 1.5%) and coma (RTLE 4.6%).

4.2.3.6. Postictal Motor and Autonomic Semiology

From the end of the electrical discharge to regaining the capacity to answer correctly to the cognitive and behavioral testing patients presented motor signs and symptoms. Motor signs and symptoms occurred in 60.6 % of the case in the RTLE, in 63.2% of the LFLE group, and in 55.6% of the RFLE group (figure 5). Motor restless was a sign that was statistically significant more common in the LFLE group in relation to the LTLE group ($p < 0.05$) (table 12).

Figure 5. Number of Postictal Motor and Autonomic Signs and Symptoms

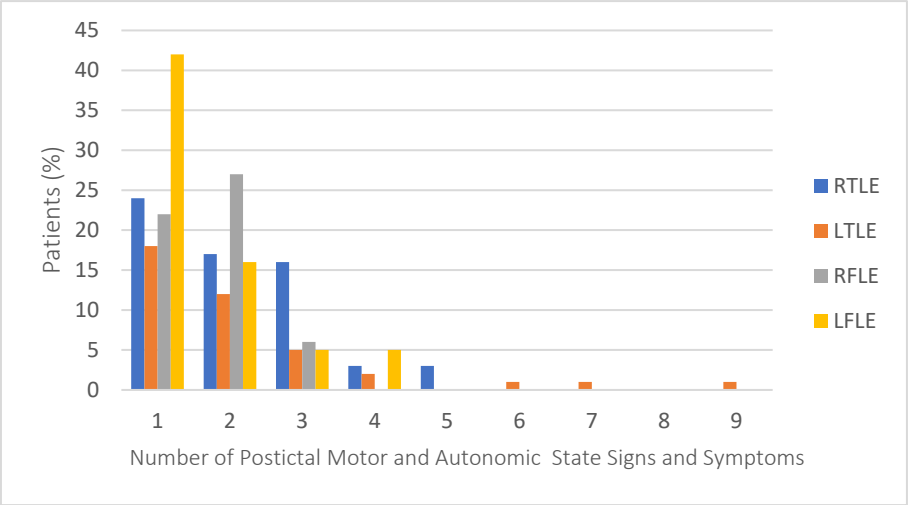


Table 12. Postictal Motor and Autonomic Semiology (PS)

Signs and Symptoms	*Location*							
	Temporal				*Frontal*			
	Right		*Left*		*Right*		*Left*	
	n (PS)	n (%)	n (PS)	n (%)	n (PS)	n (%)	n (PS)	n (%)
Manual Automatisms	13	19.7	15	17.6	5	27.8	2	10.5
Oral Automatisms	18	27.3	15	17.6	2	11.1	5	26.3
Smacking	1	1.5	3	3.5	1	5.6	0	0
Laughing	2	3.0	4	4.7	4	22.2	0	0
Coughs	21**	31.8	7**	8.2	6*	33.3	2*	10.5
Nose-rubbing	19	28.8	22	25.9	2	11.1	2	10.5
Gape	2	3.0	0	0	0	0	0	0
Hiccup	1	1.5	0	0	0	0	1	5.3
Verbal automatisms	1	1.5	0	0	0	0	0	0
Motor restless	2	3.0	6*	7.2	1	5.6	4*	21.1

*= $p < 0.05$ for RFLE and LFLE, LTLE and LFLE
**= $p < 0.01$ for RTLE and LTLE

Postictal coughing was present in all groups, being statistically significant more common in the right hemisphere. In the RTLE group in relation to the LTLE group p-value was $p < 0.01$, and in the RFLE group in relation to the LFLE group was $p < 0.05$.

After seizure 18.9% of the patients with RTLE had the first cough at a mean time of 18.5 ± 18.3 seconds (range, 2 to 63 seconds), being statistically significant earlier ($p < 0.05$) than in patients

with LTLE (9,4%) who had their first cough at a mean time of 39.6 ± 28.5 seconds (range, 17 to 104 seconds). In the RTLE group the second cough was at 34.1 ± 22.4 seconds (n = 7; range, 7 to 74 seconds) and the third cough at 43.0 ± 1.0 seconds (n = 2; range, 42 to 44 seconds). In the LTLE group two patients had a second cough at 24 seconds, and one patient had four coughs, second cough at 133 seconds, third at 184 seconds and fourth at 190 seconds.

In the RFLE group 16.7% of the patients had the first cough at a mean time of 33.7 ± 13.0 seconds (range, 23 to 52 seconds), and one patient had three coughs, the second at 53 seconds and the third at 105 seconds. In the LFLE group 10,5% of the patients had coughs after seizure. In relation to the time of the first cough of the other three groups, in the LFLE group the time after seizure until the first cough was the longest at a mean time of 64.5 ± 28.5 seconds (range, 36 to 93 seconds) and this patients had only one cough.

In the RTLE group patients with right laterality (n = 9) had one cough after ictal state, ambidextrous patients (n = 2) two coughs and one left-handed patient three coughs. In the RFLE group three patients had coughs and were right-handed. In the LTLE seven patients were right-handed and one left-handed.

4.2.3.7. Postictal Language Manifestations

Thirty-one patients (16.5%) had aphasia during the postictal state. Postictal aphasia duration (time from seizure end to regaining the ability to name objects) ranged from 18 to 707 second. Patients with LTLE with right-handed laterality (n = 26) needed a mean time of 250.9 ± 192.2 seconds (range, 29 to 770 seconds) to be able to name objects correctly. Also patients with RTLE presented aphasia, four right-handed patients needed a mean time of 149.4 ± 67.4 seconds (range, 52 to 233) and one ambidextrous patient (who had three seizures with aphasia) required a mean time of 81.0 ± 31.1 seconds (range, 47 to 108 seconds) to be able to name the objects that were presented. In all patients with right-sided epilepsy and postictal aphasia, either a large brain defect (trauma) or a diffuse, widely spread pathology was present on the right, so that seizure spread to the left hemisphere was suspected, even though on surface EEG this could not be documented in all cases.

Partial dysnomia (fluctuation of ability to name objects) was observed in 17 patients with LTLE: 14 patients were right-handed, two ambidextrous and one left-handed. Right-handed patients needed a mean time of mean 436.5± 243.2 seconds to be able to name objects (range, 138 to

970 seconds), ambidextrous patients a mean time of 956.5 ± 242.5 seconds (range, 785 to 1128 seconds), and one left-handed patient 336 seconds. Also two patients with RTLE presented partial dysnomia: one patient was right-handed and required 63 seconds to name objects, and one patient (who had two seizures with partial dysnomia) was ambidextrous and needed a mean time of 323.0 ± 196.6 seconds (range, 314 to 592 seconds) to be able to name objects correctly, as above, these patients had documented spread to the left hemisphere.

Four patients had first aphasia and then partial dysnomia: one right-handed patient with RTLE had aphasia for 382 seconds and partial dysnomia 323 seconds, two right-handed patients with LTLE had aphasia for 250.0 ± 83.4 seconds and partial dysnomia 423.5 ± 294.9 seconds, and one left-handed patient with LTLE (who had two seizures with aphasia and partial dysnomia) had aphasia for a mean time of 971.0 ± 783.5 seconds and partial dysnomia for 475,0 ± 99,0 seconds.

4.3. Correlation between Time to Recover Consciousness and Clinical Characteristics

4.3.1. Epilepsy localization

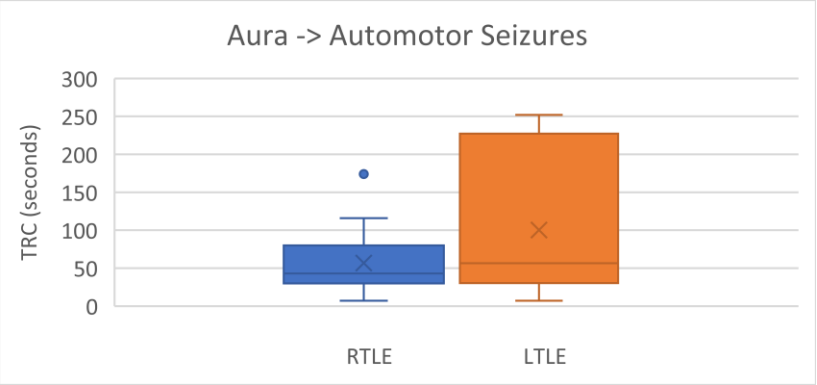
The Kruskal-Wallis test indicated that the time it takes for patients to give a first adequate response (FAR) after seizure was statistically significantly different between the four groups ($p = .012$). Patients with left hemisphere epilepsy onset had a statistically significant difference in the time they needed to RC ($p < 0.01$). The LTLE group needed more time to RC with a mean rank time of 107.0 seconds than the LFLE group with 68.9 seconds. On the other hand, patients with right hemisphere lateralization the mean rank to RC was not statistically significant different with 88.9 seconds for the RTLE group and 76.6 seconds for the RFLE group.

4.3.2. Epileptic Seizure Types

Seizures that begin with an aura and develop to an automotor seizures were present in 26.7% of the patients with RTLE, and 16.5% of the patients with LTLE. Patients with RTLE needed a mean time of 60.4 ± 45.0 seconds to give an adequate answer and patients with LTLE required 95.8 ± 91.9 seconds to give the first adequate answer. When this type of seizure develops to a second seizure such as versive seizure patients with RTLE required seven seconds and with LTLE 115 seconds postictally to RC. If the second seizure was a complex-motor seizure patient with RTLE

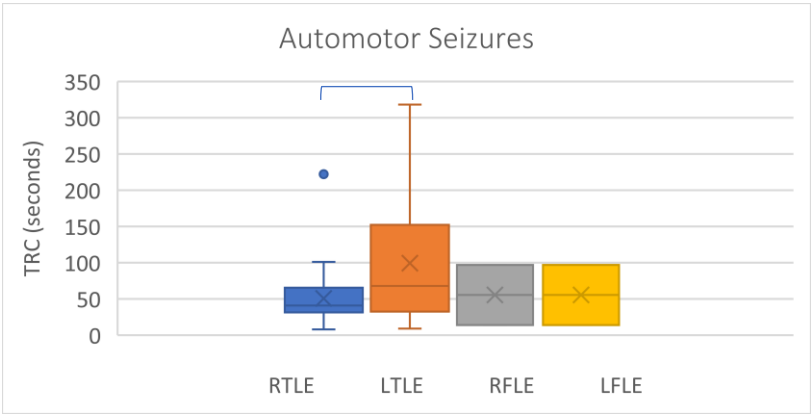
needed 239 seconds and with LTLE 14 seconds to RC. In one patient with aura -> automotor seizure develop to a left clonic seizure taking 59 seconds to be able to give an adequate answer (figure 6).

Figure 6. Aura -> Automotor Seizures and Time to Recover Consciousness in the RTLE and LTLE groups



Patients with automotor seizures with RFLE onset (n = 4) needed a mean time of 117.8 ± 154.3 seconds to RC, with LTLE (n = 31) onset 96.9 ± 65.0 seconds, with LFLE (n = 3) 78.0 ± 78.0 seconds and with RTLE (n = 32) 53.9 ± 40.5 seconds. Patients with LTLE needed statistically significant more TRC than patients with RTLE, when the patients were divided in right and left hemisphere groups this statistical difference was maintained ($p < 0.05$) (figure 7).

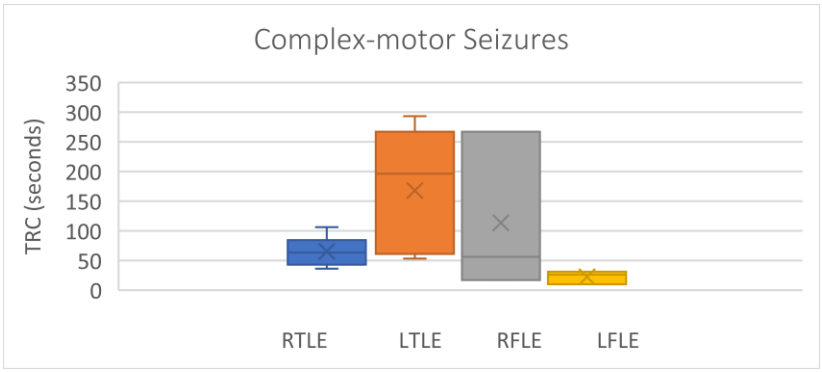
Figure 7. Automotor Seizures and Time to Recover Consciousness



*= $p < 0.05$ for LTLE vs. RTLE
$p < 0.05$ for left hemisphere vs. right hemisphere

RC in patients with complex-motor seizures was longer than in automotor seizures in patients with RFLE (n = 3) with a mean time of 113.3 ± 134.5 seconds and for patients with LTLE (n =8) 167.6 ± 106.0 seconds. Patients with RTLE (n =7) with complex-motor seizure developed to one or two more seizures the time to RC was 56.9 ± 32.5 seconds. Only LFLE patients (n = 3) required less time to give a FAR in the postictal state (mean 22.3 ± 11.0 seconds) (figure 8).

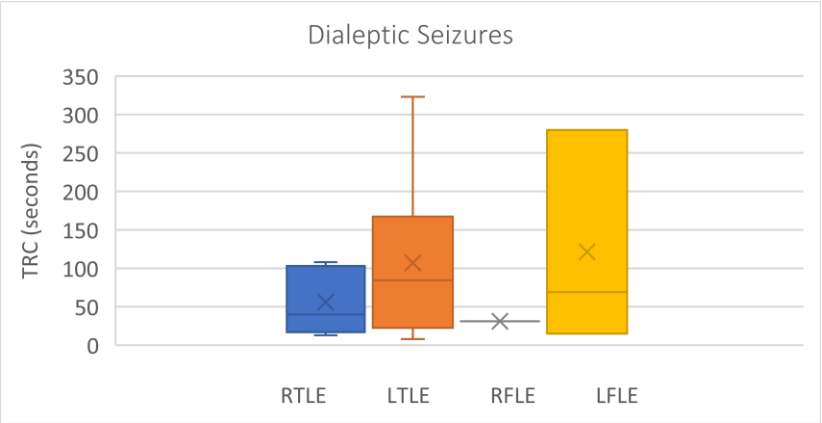
Figure 8. Complex-motor Seizures and Duration to Recover Consciousness



Hypermotor seizures were rare, only four patients presented them and the duration to RC was shorter than automotor and complex-motor seizures. In the LFLE group, three patients needed a mean time of 12.3 ± 4.9 seconds to RC and in the RFLE group, one patient required 26 seconds. Because of the small group size for this semiological sign, statistical analysis was not available.

On the other hand, in patients with dialeptic seizures, the duration to RC in the LTLE group (n = 13) was 94.9 ± 95.7 seconds, in the RTLE group (n = 4) 60.0 ± 49.9 seconds, in the RFLE group (n = 1) 31 seconds, and in the LFLE group (n = 1) 69 seconds, without statistically significance between the RTLE and LTLE groups. In the RTLE group, one patient had a dialeptic seizure and an automotor seizure and required 40 seconds to give the FAR, and one patient with an aura + dialeptic seizure + tonic seizure needed 218 seconds to RC. In the LTLE group, three patients were diagnosed with dialeptic -> automotor seizure taking a mean duration of 35.0 ± 14.9 seconds to RC. In the LFLE group, one patient had a dialeptic seizure -> aphasic seizure and required 15 seconds to RC, and another patient had a dialeptic seizure -> automotoric seizure 280 seconds to RC (figure 9).

Figure 9. Dialeptic Seizures and Time to Recover Consciousness



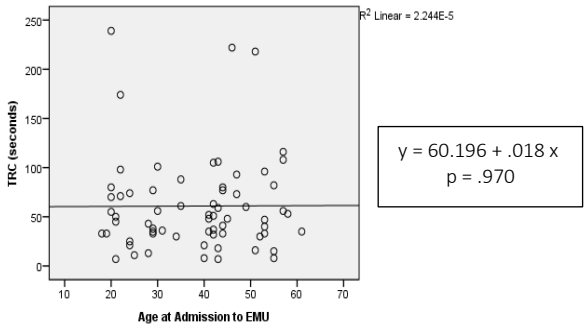
In other seizure types, in the LTLE group patients diagnosed with aphasic seizures (n = 2) needed more time to give a FAR (mean 202.5 ± 110.5 seconds) than patients diagnosed with aura -> aphasic seizure (n = 2, mean 71.0 ± 51.0 seconds). One patient was diagnosed with aura -> versive left seizure -> automotor seizure and required 84 seconds to RC. In the RTLE group three patients had vegetative seizure that develop to an automotor seizure needing a mean time 49.7 ± 33.2 seconds to RC. In the RFLE group four patients had tonic seizures that develop to hypermotor or complex-motor seizure taking a mean time of 64.0 ± 18.8 seconds to RC.

4.3.3. Age at Admission to the EMU

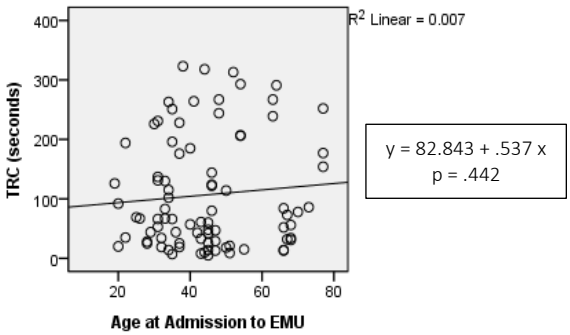
The age at admission in patients with LTLE and RFLE had a positive relation with the time to regain consciousness, as the age of admission increased patients needed more time to RC. In the LFLE group the relation was negative, and in the RTLE group there was no relation (figure 10).

Figure 10. Scatter plots between TFAR and the variable Age at Admission

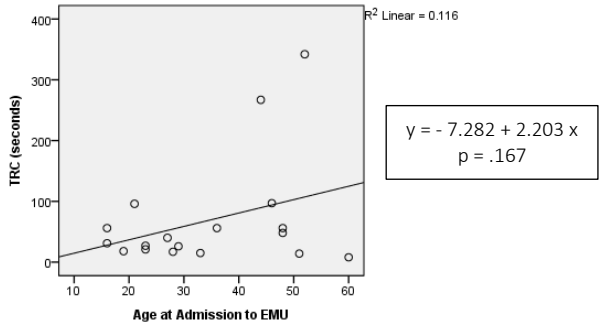
RTLE



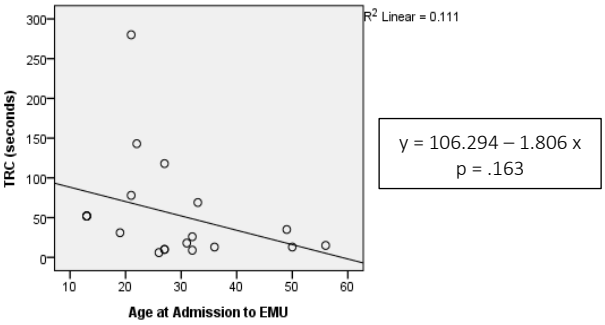
LTLE



RFLE



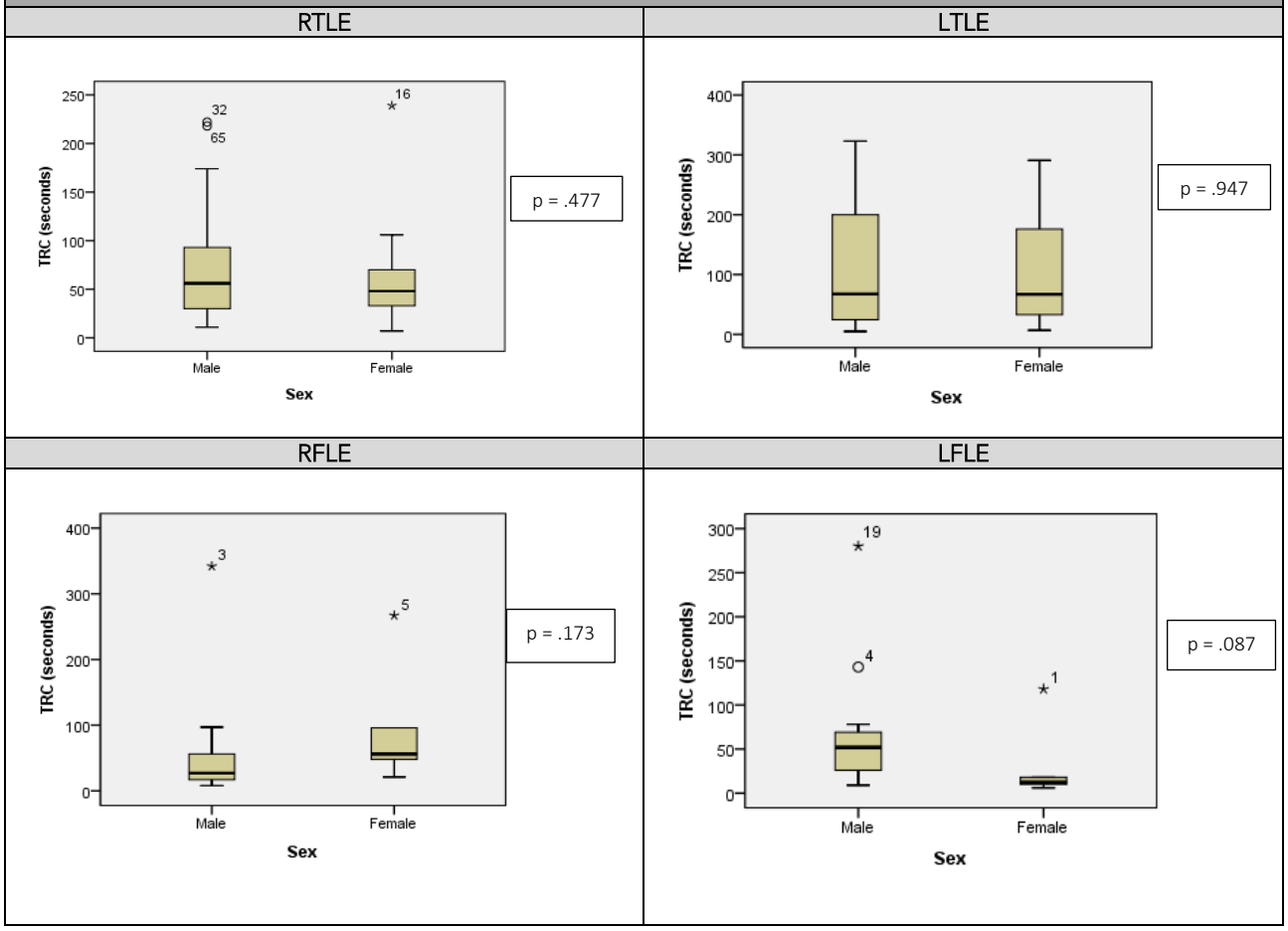
LFLE



4.3.4. Sex

Males (mean 113.0 ± 103.9 seconds) and females (mean 102.3 ± 86.4 seconds) with LTLE needed more time to RC compared to RTLE males (69.1 ± 56.3 seconds) and females (54.5 ± 40.8 seconds), RFLE males (57.5 ± 88.9 seconds) and females (97.6 ± 98.4 seconds) and LFLE males (65.6 ± 73.7 seconds) and females (29.5 ± 4.6 seconds). Duration to give the FAR after ictal state was not statistically significant between males and females in the four groups (figure 11).

Figure 11. Distribution duration to RC and Sex with statistical significance



4.3.5. Laterality

The duration to recover consciousness in patients with ambidextrous laterality and left hemisphere epilepsy was the longest (mean 139.8 ± 126.1 seconds) and had a difference of 105 seconds in relation to patients with right hemisphere epilepsy (mean 34.5 ± 22.4 seconds).

Patients with right-handed laterality required statistically significant more time when the epilepsy onset was in the left hemisphere (mean 106.7 ± 92.0 seconds) in relation to the right hemisphere (mean 69.6 ± 54.9 seconds) ($p < 0.05$). On the other hand, patients with left-handed laterality respond earlier to the cognitive and behavioral evaluation, if they had a left hemisphere seizure onset, they needed 47.7 ± 40.8 seconds to give an adequate response, and with right hemisphere onset 57.1 ± 74.5 seconds.

Table 13 shows the distribution of TRC according to laterality and epilepsy onset in the four groups.

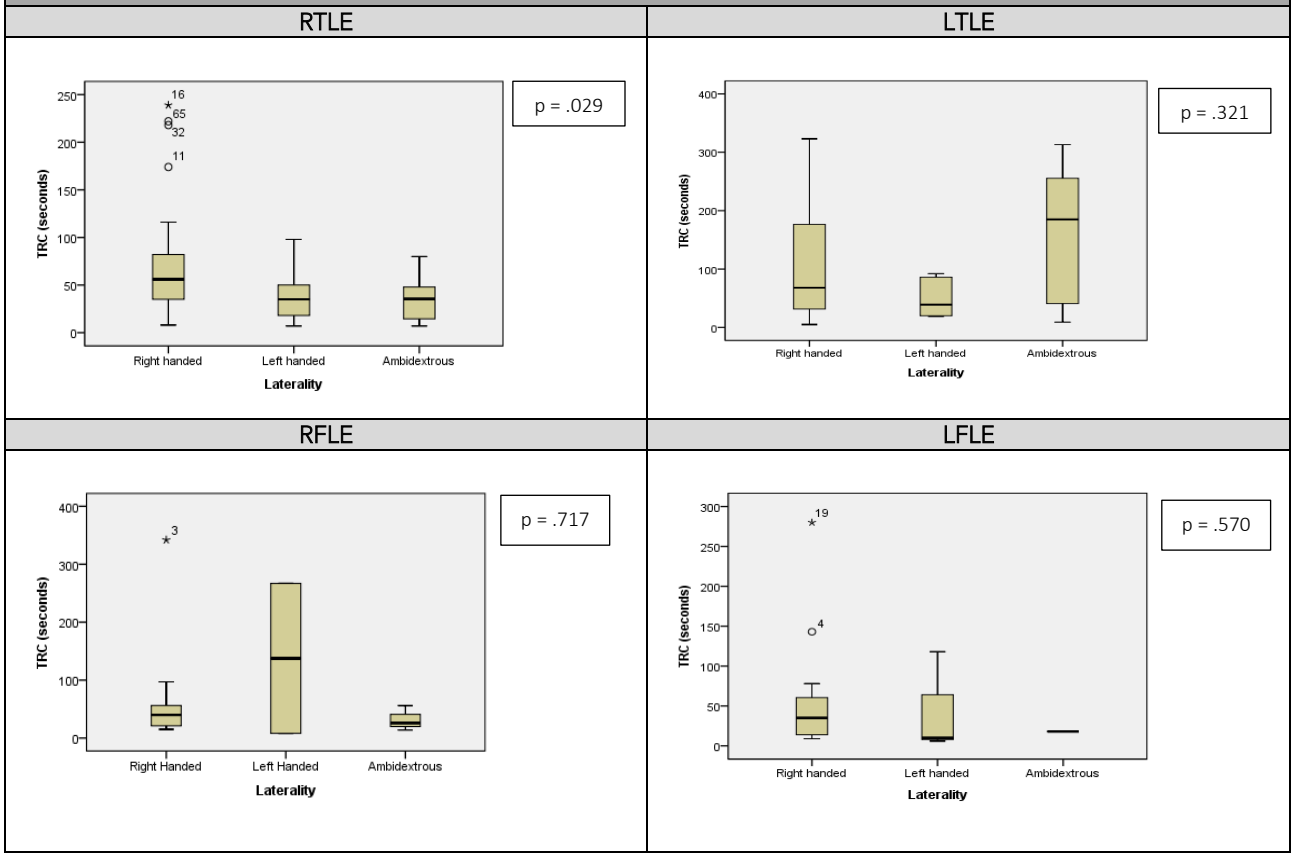
Table 13. Distribution of TRC according to Laterality and Localization

			Seconds				
Hemisphere	Lobe	Laterality	Mean	SD	Median	Minimum	Maximum
Right	*Temporal*	Right	69.6**	54.9	56	7	239
		Left	39.2**	27.6	35	7	98
		Ambidextrous	35.4**	24.1	36	7	80
	Frontal	Right	66.5	87.2	40	15	342
		Left	137.5	183.1	138	8	267
		Ambidextrous	32.0	21.6	26	14	56
Left	*Temporal*	Right	106.7*	92.0	68	5	323
		Left	49.2	32.3	39	19	92
		Ambidextrous	157.1	125.4	185	9	313
	Frontal	Right	58.5	70.7	35	9	280
		Left	44.7	63.5	10	6	118
		Ambidextrous	18.0	0.0	18	18	18

*= $p < 0.05$ for right hemisphere vs left hemisphere right-handed patients
**= $p < 0.05$ for RTLE right-handed patients vs left-handed and ambidextrous patients

In the RTLE group time to RC had a statistically significant difference according to the laterality of the patients ($p < 0.05$). Right-handed patients required more time to give a FAR (MR = 37.18) than left-handed (MR = 23.94) and ambidextrous patients (MR = 21.69). In the LTLE group patients with ambidextrous laterality required more time to RC (MR = 51.50) than right-handed (MR = 43.18) and left-handed patients (MR = 30.92). In the RFLE group were right-handed (MR = 10.08) followed by left-handed (MR = 9.00) and ambidextrous patients (MR = 7.33). In the LFLE group, right-handed (MR = 10.70) required more time than ambidextrous (MR = 8.00) and left-handed (MR = 7.17) patients (figure 12).

Figure 12. Distribution of TRC according to Laterality

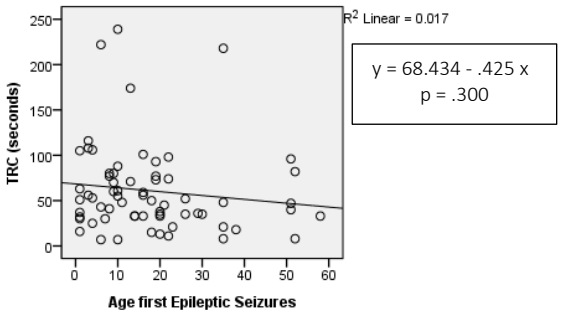


4.3.6. Age at Epilepsy Onset

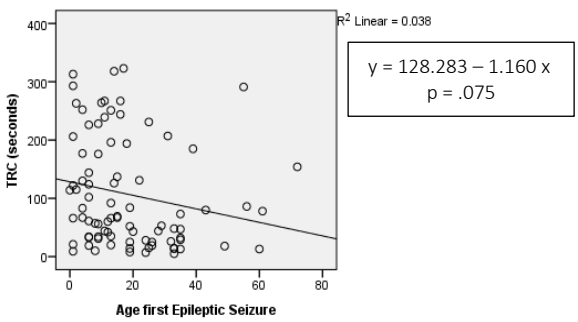
There was a positive correlation between the duration to give a FAR with the age at epilepsy onset in patients with RFLE and a negative correlation in patients with LTLE (figure 13).

Figure 13. Scatter plots between TRC and the variable Age at Epilepsy Onset

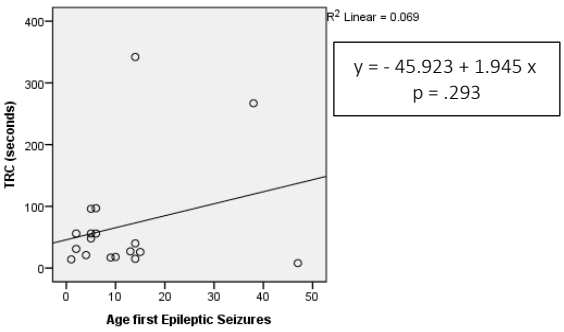
RTLE



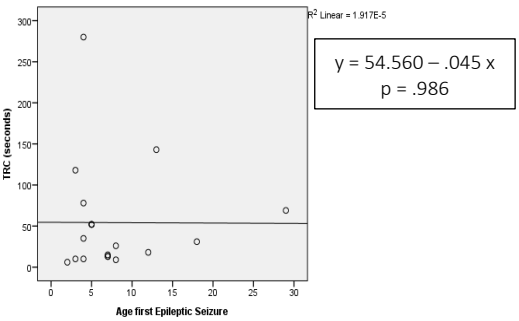
LTLE



RFLE

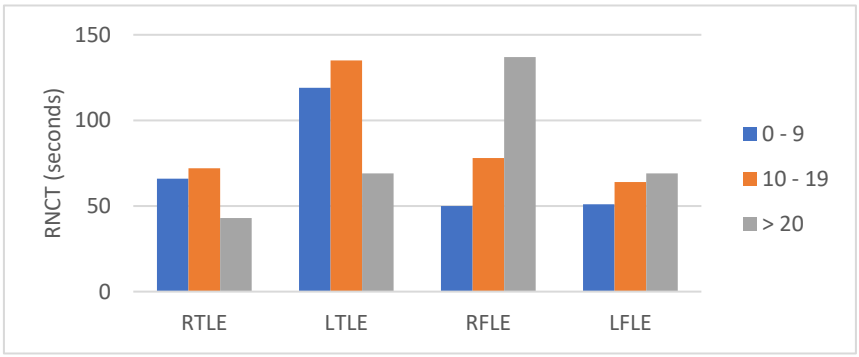


LFLE



Dividing the groups by range of ages 0 to 9 years, 10 to 19 years, and > 20 years in frontal lobe patients the RC time increased when patients were older. For the RFLE group patients from the first range of age needed a mean time of 49.2 ± 28.3 seconds to RC, from the second range required a mean time of 77.8 ± 118.2 seconds and from the third range of age a mean time of 137.3 ± 129.8 seconds. In the LFLE group the time to RC was 51.3 ± 68.3 seconds, 64.0 ± 56.1 seconds and 69 seconds, respectively. On the other hand, in temporal lobe patients time to regain consciousness was longer in the first two groups of age ranges, with right hemisphere onset for the first range of age was 65.5 ± 45.8 seconds and for the second range of age was 71.9 ± 53.2 seconds, and with left hemisphere onset 118.9 ± 88.7 seconds and 134.8 ± 103.3 seconds, respectively. In this two last groups patients needed less time to RC, when the epilepsy onset was after 20 years (RTLE, mean 43.3 ± 45.8 seconds; LTLE, mean 69.3 ± 74.0 seconds) (figure 14).

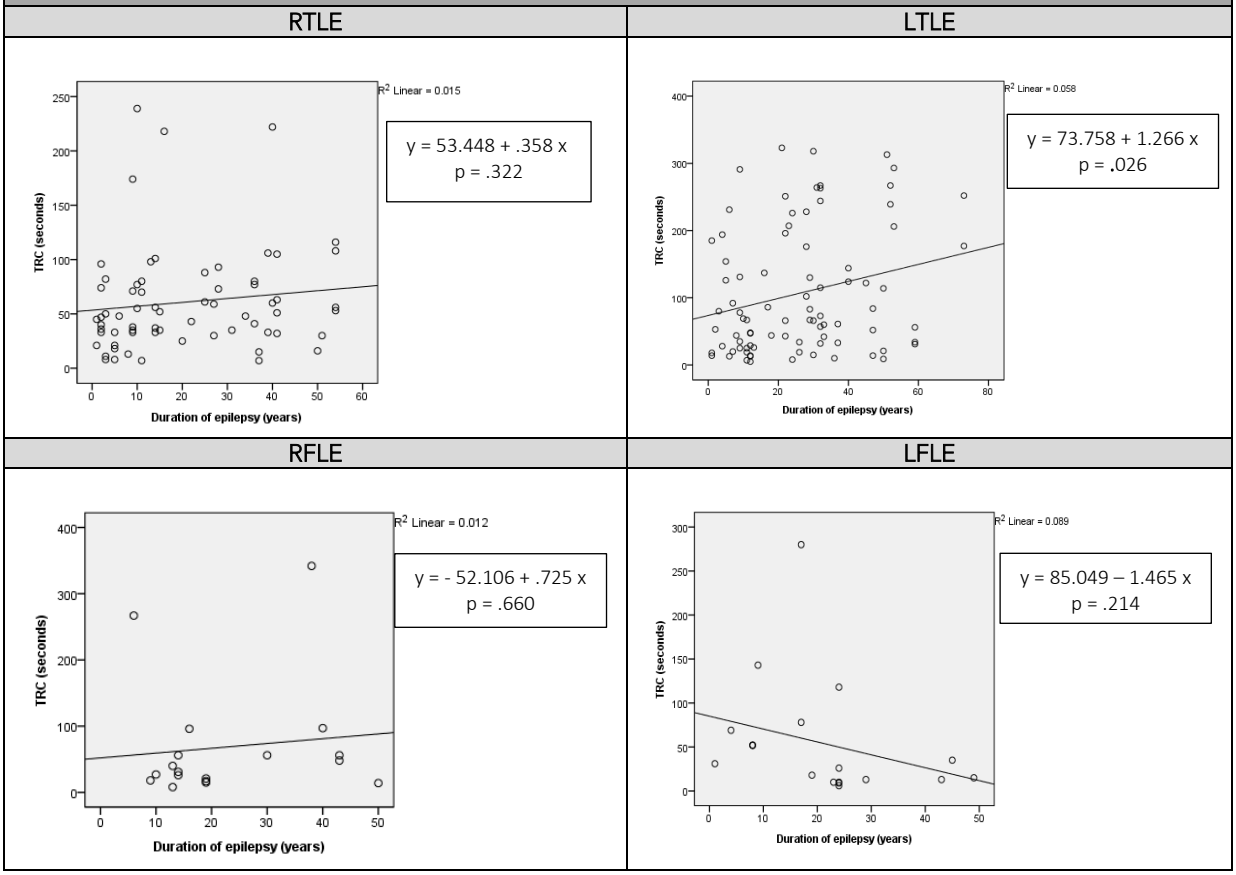
Figure 14. Distribution of TRC according to Age at Epilepsy Onset



4.3.7. Duration of Epilepsy

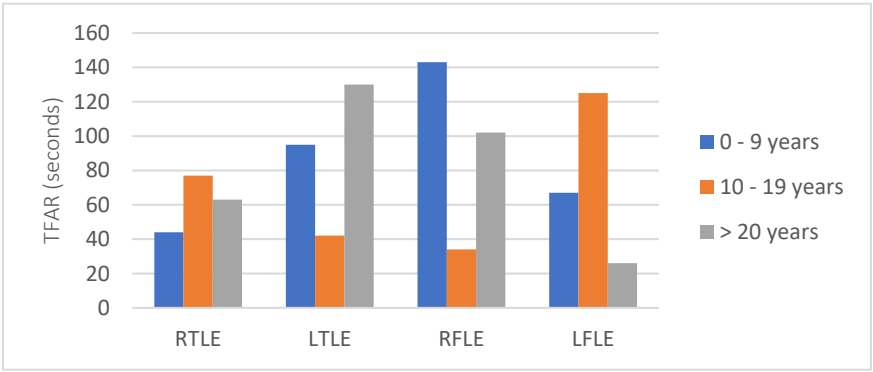
In the LTLE group the variable duration of epilepsy had a statistically significant influence in the capacity of the patient to RC, as the years with epilepsy increases the time that patients need to be able to give the FAR raises ($p < 0.05$). In the RTLE and RFLE groups the duration of epilepsy had a positive relation to the time patients needed to RC, without a statistically significance. For the LFLE group the correlation was negative, as the years of evolution increase, the duration to give the FAR is shorter (figure 15).

Figure 15. Scatter plots between TRC and Duration of Epilepsy



Time to regain consciousness was longer in patients with RTLE and LFLE when the duration of epilepsy was from 10 to 19 years (RTLE, mean 76.5 ± 69.9 seconds; LFLE, mean 125.3 ± 112.1 seconds). In patients with RFLE was from 0 to 9 years (mean 142.5 ± 124.5 seconds) and in patients with LTLE was having epilepsy over 20 years (mean 130.0 ± 99.5 seconds) (figure 16).

Figure 16. Distribution of TFAR according to Duration of Epilepsy

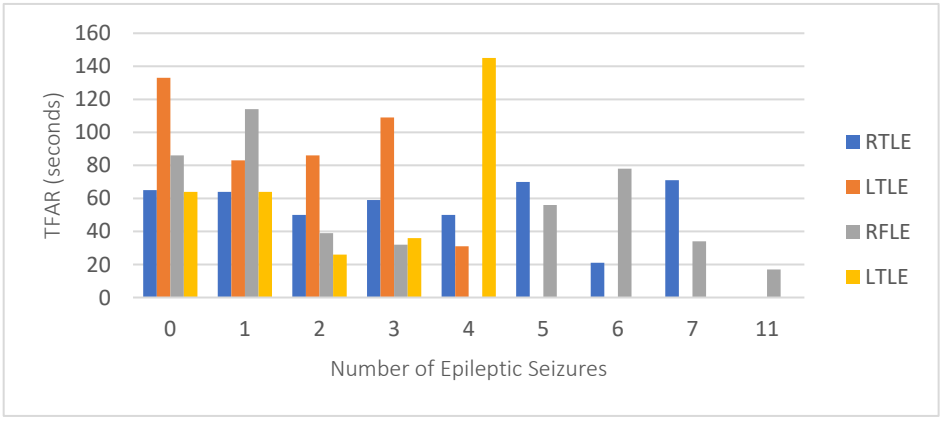


4.4. Correlation between Time in Regaining Consciousness and the Characteristics of the Seizure

4.4.1. Amount of Epileptic Seizures on the same day before the analyzed Seizure

In the four groups the number of epileptic seizures on the same day before the analyzed seizure has no influence in the duration of RC. In each group the longest duration was different. For patients with LTLE was not having epileptic seizures before the analyzed epileptic seizure (mean 132.6 ± 105.4 seconds), for patients with RFLE was one epileptic seizure (mean 114.0 ± 132.9 seconds), for patients with LFLE four epileptic seizures (mean 145.0 ± 190.9 seconds) and for one patient with RTLE seven epileptic seizures (71 seconds) (figure 17).

Figure 17. Distribution of TFAR according to the variable Amount of Epileptic Seizures on the same day before the analyzed Seizure



4.4.2. State of Consciousness before the Seizure

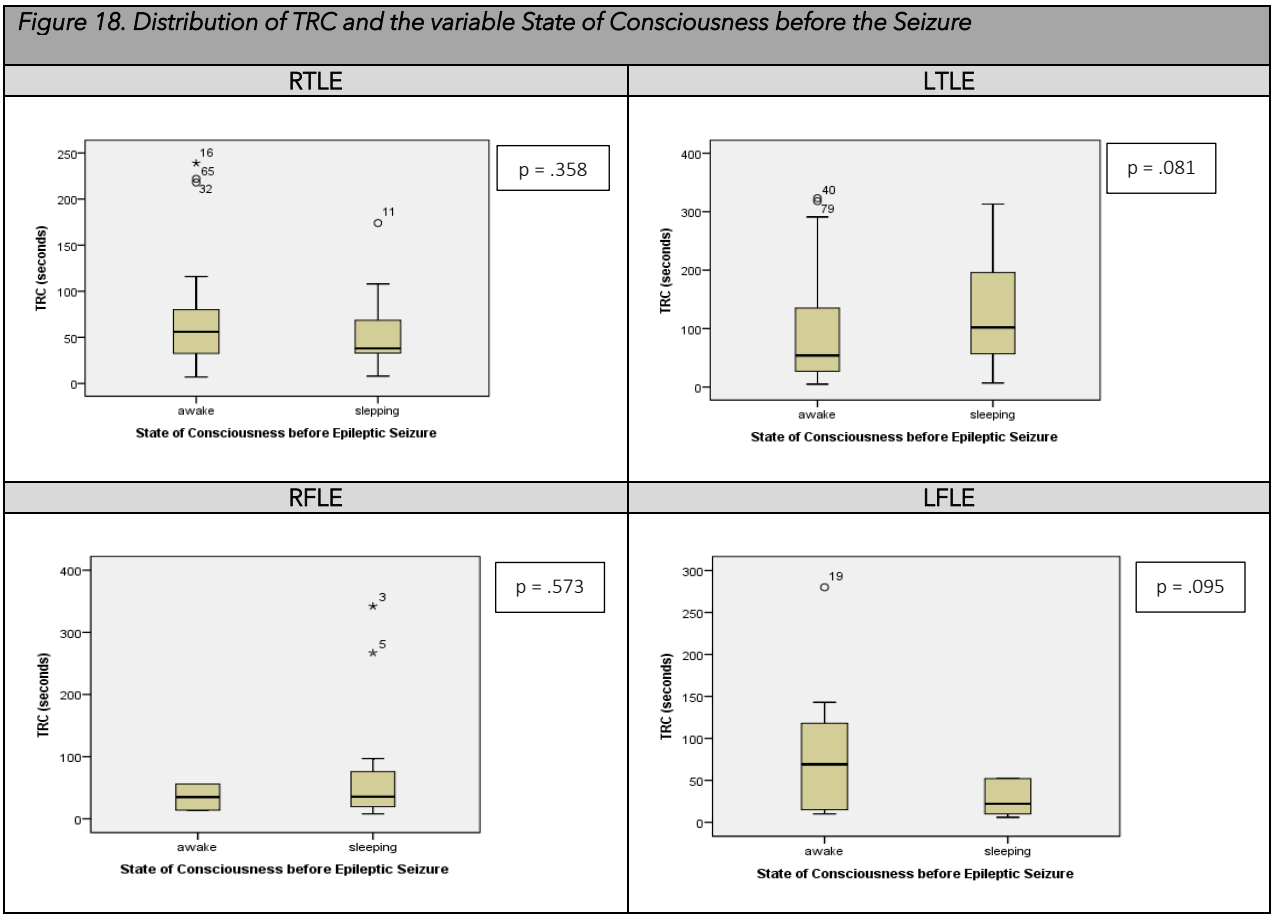
In general, there was no statistically significant difference in the duration of RC in patients that were awake or sleeping before the epileptic seizure. Although analyzing this variables in each of the four groups, some distinction can be appreciated.

Awake patients needed from 5 to 323 seconds to give the FAR during postictal state. Patients with left hemisphere epilepsy with temporal onset required a mean time of 96.2 ± 93.2 seconds and with frontal onset 84.1 ± 87.6 seconds to give the FAR. Right hemisphere patients with

temporal onset took 66.3 ± 54.7 seconds and with frontal onset 35.0 ± 29.7 seconds to give a FAR.

Patients that were sleeping before the epileptic seizure required from 7 to 313 seconds to RC. The LTLE group needed more time to be able to give a correct answer, taking a mean time of 127.3 ± 92.9 seconds, similar time as the patients that were awake before the seizure. In the other hand, the LFLE patients that were sleeping were faster to answer to the technicians instructions (mean 27.3 ± 19.1 seconds) in relation to LFLE awake patients and the other patients. Patients with right hemisphere epilepsy with frontal onset needed a mean time of 72.8 ± 95.2 seconds, and with temporal onset 53.0 ± 36.8 seconds to RC (figure 18).

Figure 18. Distribution of TRC and the variable State of Consciousness before the Seizure



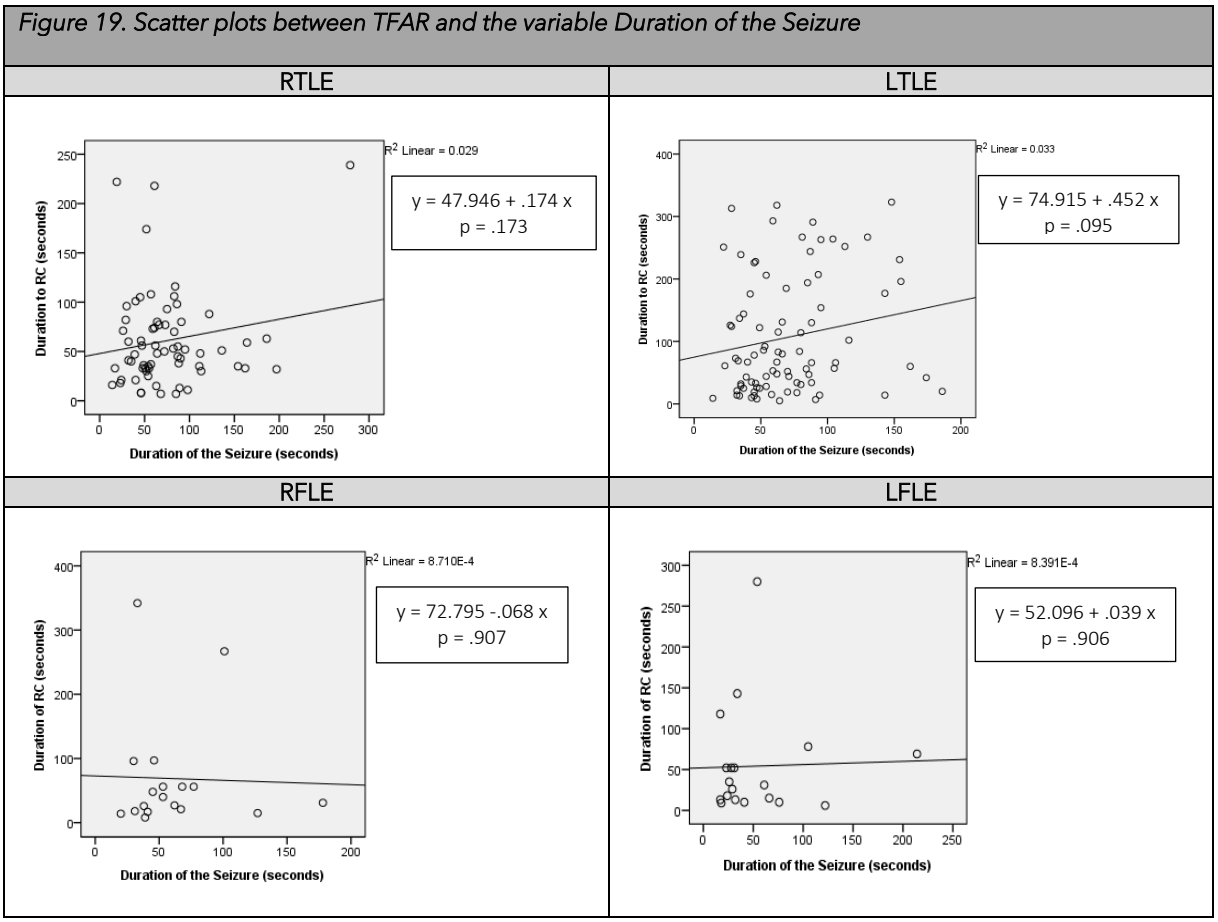
4.4.3. Duration of the Seizure

On a descriptive level it was observed that in the LTLE group seizure time was shorter (mean 70.5 ± 37.7 seconds) than the time patients needed to give the FAR (mean 106.8 ± 93.7 seconds). On the other hand, for patients with RTLE duration of the seizure (mean 74.4 ± 47.2 seconds) was slightly longer than the time patients needed to RC (mean 60.9 ± 48.3 seconds).

For patients with frontal lobe epilepsy duration of the seizure and time to recover consciousness were nearly the same. In the RFLE group seizure mean duration was 61.6 ± 39.4 seconds and RC mean duration was 68.6 ± 90.5 seconds. In the LFLE group seizure mean duration was 53.6 ± 48.9 seconds and TRC duration 54.2 ± 66.6 seconds. The difference in time to recover consciousness between LTLE and the other groups did not correlate with seizure duration.

Figure 19 shows a positive relation between seizure duration and the duration to give an FAR in patients with temporal lobe epilepsy. In patients with frontal lobe epilepsy the duration of the seizure and TRC was the same.

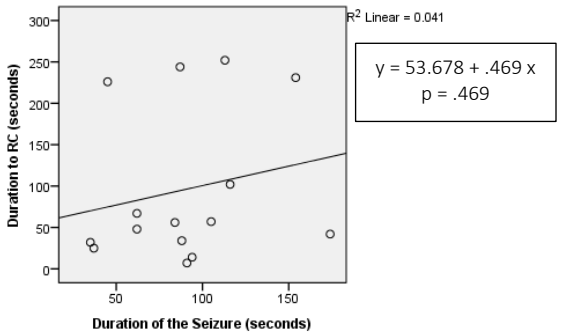
Figure 19. Scatter plots between TFAR and the variable Duration of the Seizure



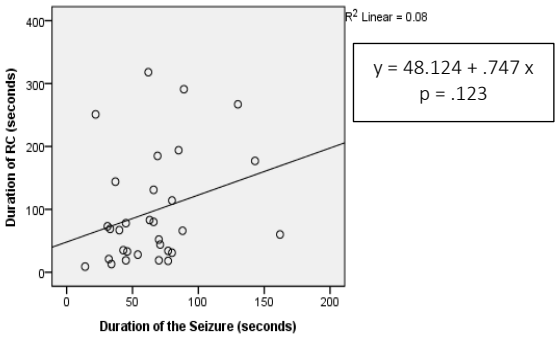
Analyzing the influence of the duration of the seizure in the time to regain consciousness during postictal state in automotor seizures, with or without aura, in complex-motor seizures and in dialeptic seizures in patients with LTLE the relation of this two variables was positive, the increase of the seizure duration prolonged the reaction time to give a FAR during the postictal state (figure 20).

Figure 20. Scatter plots of TFAR in LTLE Seizures and the variable Duration of the Seizure

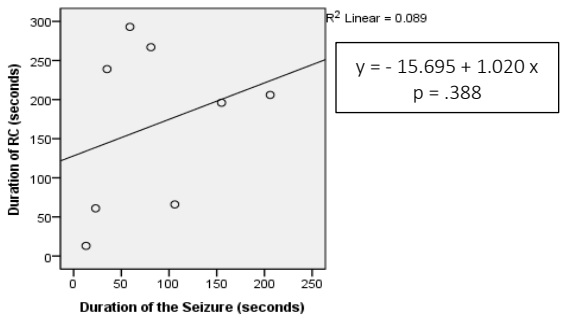
Aura -> Automotor Seizures



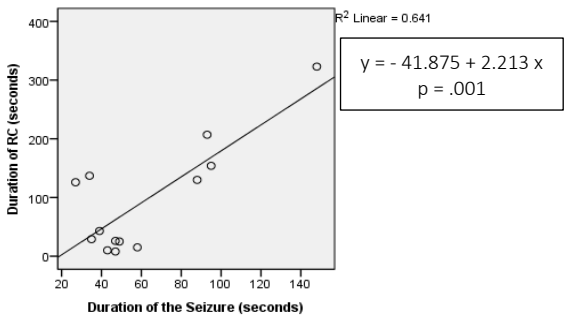
Automotor Seizures



Complex-motor Seizures



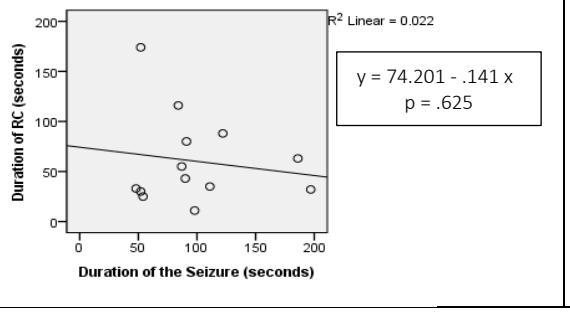
Dialeptic Seizures



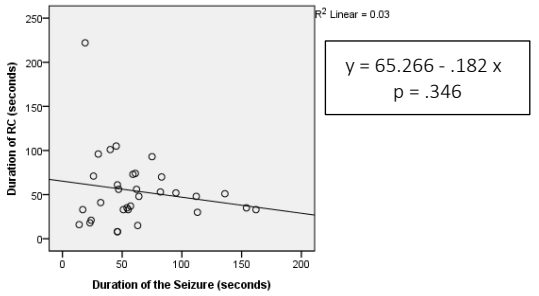
In dialeptic seizures this positive relation was statistically significant. On the other hand, in patients with RTLE the relation between this two variables were negative (figure 21).

Figure 21. Scatter plots between TRC in RTLE Seizures and the variable Duration of Seizure

Aura -> Automotor Seizure



Automotor Seizure



4.4.4. Seizure Semiology

Table 14 shows that 72.7% of the patients with RTLE and 70.6% of the patients with LTLE presented signs and symptoms during the seizure. RTLE had up to seven signs and symptoms

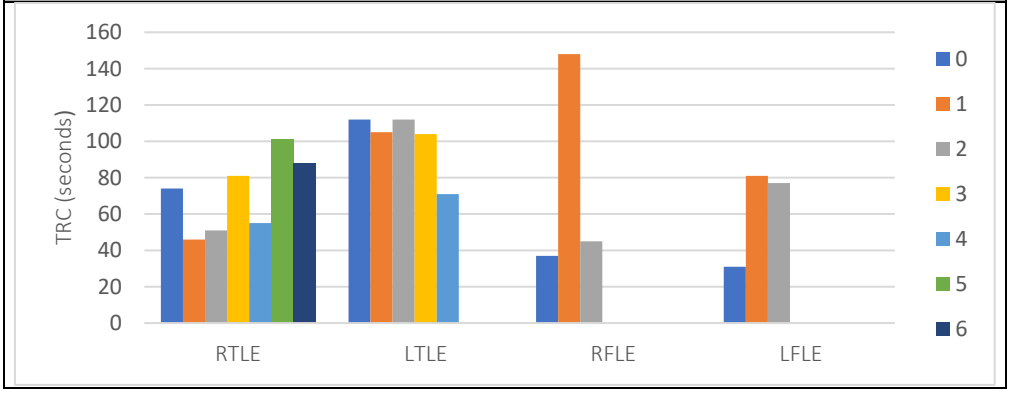
and LTLE up to four. On the other hand, less than half of the patients with frontal lobe epilepsy had signs and symptoms during the seizure. Patients with right onset were 33.3% and with left onset 47.4%. Both groups of patients had up to two signs and symptoms (figure 22).

Patients with TLE with ictal signs needed a similar time to RC as patients without signs and symptoms. Only when the patients had four signs and symptoms time to RC was shorter than patients without signs and symptoms. On the contrary, patients with FLE required more time to RC when they had signs and symptoms (table 15). There was no statistically significant relationship between the RC mean time when patients of the four groups present one sign or symptom or between the temporal groups in two signs and symptoms.

Table 14. Distribution of TRC according to Signs and Symptoms of the Ictal State (SSIS)

					Seconds		
SSIS	Lobe	Laterality	N	%	Mean	SD	Median
All	*Temporal*	Right	48	72.7	55.3	44.7	48
		Left	60	70.6	10.8	90.8	67
	Frontal	Right	6	33.3	131.0	127.3	73
		Left	9	47.4	80.1	83.2	52
0	*Temporal*	Right	18	27.3	73.8	45.0	65
		Left	25	29.4	111.6	98.5	73
	Frontal	Right	12	66.7	37.3	23.9	29
		Left	10	52.6	30.9	25.0	17
1	*Temporal*	Right	25	37.9	45.5	26.1	45
		Left	31	36.5	105.0	95.2	67
	Frontal	Right	5	27.8	147.6	149.4	97
		Left	7	36.8	81.1	94.3	52
2	*Temporal*	Right	7	10.6	51.4	38.0	37
		Left	16	18.8	111.7	99.4	59
	Frontal	Right	1	5.6	45.0	0	0
		Left	2	16.1	76.5	94.0	77
3	*Temporal*	Right	8	12.1	81.4	81.3	46
		Left	10	11.7	103.5	86.4	68
4	*Temporal*	Right	4	6.1	54.8	20.5	52
		Left	3	3.5	71.0	36.3	80
5	*Temporal*	Right	3	4.5	100.7	18.6	106
7	*Temporal*	Right	1	0	88	0	0

Figure 22. Distribution of TRC according to Signs and Symptoms of the Ictal State (ISSS)



4.4.5. Level of Consciousness after the Seizure

After the seizure, patients felt confused (76.6%), sleepy (9.6%), obtunded (11.7%), stuporous (0.5%) or resembled a comatose state (1.6%). In accordance with the previous results, LTLE patients were the ones that needed more time to give the FAR no matter the level of consciousness: confused (mean 96.1 ± 90.2 seconds), drowsiness (mean 123.2 ± 80.0 seconds) or obtunded (mean 189.8 ± 100.7 seconds). Though, two patients with RFLE felt obtunded needing a mean time of 219.0 ± 173.9 seconds to give an adequate answer during the postictal state (table 15).

Table 15. Distribution of TRC according to the variable Level of Consciousness after Seizure

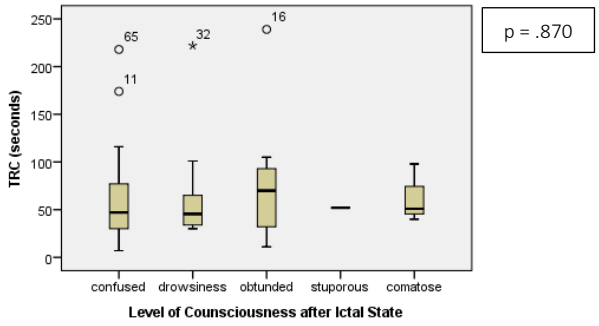
					Seconds				
Level of Consciousness	Lobe	Laterality	N	%	Mean	SD	Median	Minimum	Maximum
Confused	*Temporal*	Right	41	62.1	56.2	43.9	47	7	218
		Left	71	83.5	96.1*	90.2	60	3	318
	Frontal	Right	16	88.9	49.8**	62.3	29	8	267
		Left	16	84.2	41.4	39.9	28	6	143
Drowsiness	*Temporal*	Right	12	18.2	64.0	53.9	46	30	222
		Left	6	7.1	123.2*	80.0	107	26	226
Obtunded	*Temporal*	Right	9	13.6	78.2	68.4	70	11	239
		Left	8	9.4	189.8*	100.7	202	8	323
	Frontal	Right	2	11.1	219**	173.9	219	96	342
		Left	3	15.8	122.7	140.4	78	10	280
Stuporous	*Temporal*	Right	1	1.5	52.0	0	0	0	0
Comatose	*Temporal*	Right	3	4.6	63.0	25.2	51	40	98

*= $p < 0.05$ for LTLE obtunded vs drowsiness and confused
**= $p < 0.05$ for RFLE obtunded vs confused

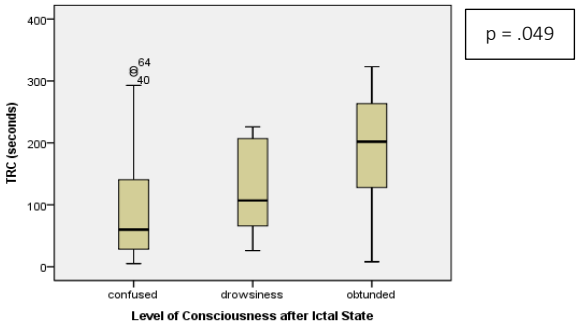
The LTLE group ($p < 0.05$) and RFLE group ($p < 0.05$) had a statistically significant difference between the different levels of consciousness. In LTLE patients that felt obtunded (MR = 61.50) need more time to RC in relation to drowsiness (MR = 50.92) and confusion (MR = 40.25). In the case of RFLE patients that felt obtunded (MR = 16.50) required more time in relation to confused patients (MR = 8.63) (figure 23).

Figure 23. Distribution of TRC and the variable Level of Consciousness after Seizure

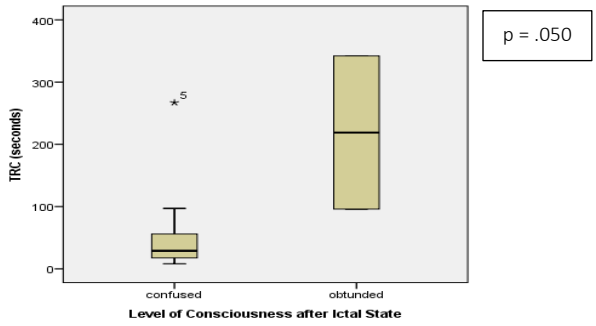
RTLE



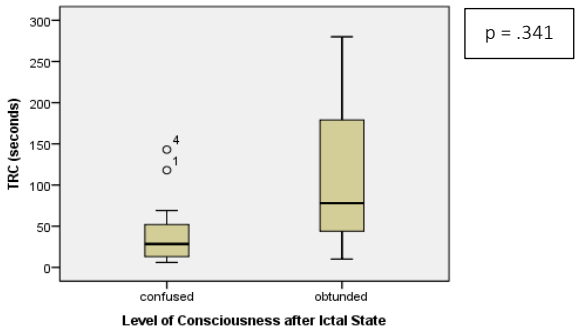
LTLE



RFLE



LFLE



4.4.6. Signs and Symptoms of the Postictal State

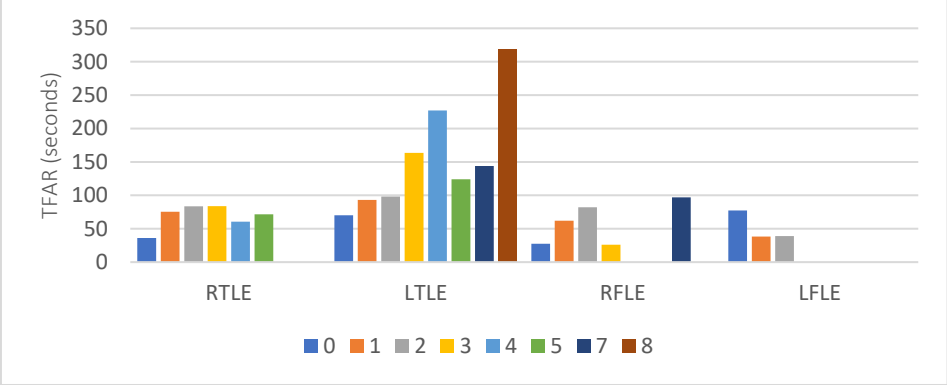
Temporal lobe epilepsy patients had more postictal signs and symptoms in relation to frontal lobe patients. Patients with LTLE had maximally eight postictal signs and symptoms until given the FAR, RTLE five, RFLE three (one patient had seven) and LFLE two. Table 16 shows that the LTLE group needed more time to RC in relation to the RTLE, LFLE and RFLE groups.

Table 16. Distribution of TFAR according to Signs and Symptoms of the Postictal State

					Seconds		
SSPS	Lobe	Laterality	N	%	Mean	SD	Median
0	*Temporal*	Right	28	42.4	36.0	25.5	34
		Left	19	22.4	70.1	77.6	35
	Frontal	Right	8	44.4	27.5	16.9	24
		Left	8	42.1	77.4	97.6	26
1	*Temporal*	Right	14	21.2	75.4	52.6	61
		Left	17	20.0	93.1	91.9	52
	Frontal	Right	4	22.2	62.0	23.9	56
		Left	7	36.8	38.3	28.2	31
2	*Temporal*	Right	12	18.2	83.6	62.3	63
		Left	8	9.4	98.1	65.0	77
	Frontal	Right	4	22.2	82.0	123.4	22
		Left	3	15.8	39.0	22.5	52
3	*Temporal*	Right	8	12.1	83.8	57.9	63
		Left	4	4.7	163.5	100.5	148
	Frontal	Right	1	5.6	26.0	0	26
4	*Temporal*	Right	2	3.0	60.5	27.6	61
		Left	2	2.4	227.0	1.4	227
5	*Temporal*	Right	2	3.0	71.5	37.5	72
		Left	1	1.2	124.0	0	124
7	*Temporal*	Left	1	1.2	144.0	0	0
	Frontal	Right	1	5.6	97.0	0	0
8	*Temporal*	Left	1	1.2	318	0	0

As illustrated in figure 24 in patients with LTLE the duration to RC increases gradually from the presence of no signs and symptoms to four signs and symptoms. After five signs and symptoms a decrease in the duration of the recovery of consciousness is observed and with nine the curve rises again. In the same vein, in RTLE time was longer from no signs and symptoms to three, with four the time decreases, and in RFLE time increases until two. In the LFLE group was the opposite, patients without signs and symptoms needed more time to RC than patients with one or two signs and symptoms.

Figure 24. Distribution of TFAR according to the number of Signs of the Postictal State



Coughing was a postictal symptom in 13.3% of the patients, 10.6% had temporal lobe epilepsy and 2.7% had frontal lobe epilepsy. In patients with TLE there was no significant correlation between mean time of RC from patients that had postictal coughing and patients that did not had postictal coughing. In patients with frontal lobe epilepsy time to RC in patients with or without coughing were almost the same (table 17).

Table 17. Distribution of TFAR according to Coughing and No Coughing during Postictal State

	Coughing			No Coughing		
	n	Mean	SD	n	Mean	SD
RTLE	12	63.3	23.7	54	58.4	53.3
LTLE	8	121.1	52.3	77	105.3	96.3
RFLE	3	77.7	26.6	15	66.7	95.5
LFLE	2	50.0	19.0	17	54.7	19.0

4.4.6. Postictal Language Manifestations

Comparing the time that patients with aphasia and without aphasia during the postictal state needed to RC no statistically significant difference was found. Since testing also included non-verbal cues, this analysis was available. In the LTLE group patients with aphasia required a mean time of 107.4 ± 94.2 seconds to RC and patients without aphasia 95.7 ± 97.2 seconds. In the RTLE group patients with aphasia required a mean time of 51.0 ± 17.1 seconds to RC and patients without aphasia 56.8 ± 47.9 seconds. In summary, the approximate time differences in regaining consciousness between the syndromes was very similar in aphasic and non-aphasic patients, especially the left temporal epilepsy patients were the ones with the longest recovery.

Chapter 5. Discussion

Normal consciousness allows us to be aware and respond to subjective and objective aspects of our daily life activities and needs, establish social relationships, and remember what we have done (Fisher et al., 2017b). In neurological disorders like epilepsy, consciousness can be limited during the seizure and in some extent in the postictal state, having an impact in the quality of life of the person with epilepsy and their family. For Lüders et al. (2014) during and after the epileptic seizure there will be a large variety of alterations of consciousness. These authors distinguish between alterations of consciousness and loss of consciousness. Alterations of consciousness during the epileptic seizures are auras with illusions or hallucinations, dyscognitive seizures, epileptic delirium, dialeptic seizures, and epileptic coma and stupor. To assess loss of consciousness two elements have to be present: amnesia of the event during the epileptic seizure and decrease of responsiveness or unresponsiveness to external stimuli during and after epileptic seizures. For the ILAE, consciousness is the key to classify epileptic seizures into focal seizures with or without loss of consciousness and generalized seizures, where consciousness is always lost (Fisher et al., 2017b).

As laid out in the introduction of this study, the functional neuroanatomy of consciousness as well as of the loss of consciousness has been described, but a definite and full correlate of the loss of consciousness in epilepsy is still elusive. The typical subcortical structures involved are basal forebrain, hypothalamus, thalamus, and upper-brainstem, and parts of the basal ganglia, cerebellum, and amygdala. The insula can also be part of the consciousness neuroanatomy. The cortical structures are medial frontal, anterior cingulate, posterior cingulate, and medial parietal (precuneus and retrosplenial) cortices on the medial surface, and the lateral frontal, orbital frontal, and lateral temporoparietal association cortices on the lateral surface (Bagshaw & Cavanna, 2011; Blumenfeld, 2005, 2012; Di Perri et al., 2014)

Understanding the process of recovering consciousness during the postictal state can help to improve quality of life of the persons with epilepsy, in the diagnosis of the disease and in the evaluation for epilepsy surgery. As a first step, the aim of this study is to establish the time to give the first adequate response (FAR) after the seizure and analyzed which factors influence the duration of the patients to be able to give the FAR, and if the recovery of consciousness (RC) can be used as a lateralizing sign.

The results of this study indicate that the duration to recover consciousness during the postictal state can be used as a lateralizing or localizing sign. Patients with LTLE needed more time (106.8 ± 93.7 seconds) to be able to respond adequately to the cognitive and behavioral testing in relation to patients with RTLE, RFLE and LFLE. Patients with LTLE required 38 seconds more than the patients with RFLE, 46 seconds more than patients with RTLE and 51 seconds more than patients with LFLE to recover consciousness during the postictal state. Of note, the left hemisphere patients with frontal lobe epilepsy were the first to respond to the cognitive and behavioral testing and patients with temporal lobe epilepsy the last ones. In patients with right hemisphere seizures the difference of duration was 12 seconds, being the time to recover consciousness between the time of the LTLE and LFLE groups.

A study by Helmstaedter et al. (1994) showed that people with focal seizures required between 60 to 600 seconds (SD 180 seconds) to reorient during the postictal state. In the present study people with focal seizure needed less time to reorient during the postictal state and the range of time was shorter (range, 5 to 342 seconds; SD 80 seconds). According to the localization of the epileptic zone, patients with LTLE (range, 5 to 323 seconds; SD 94 seconds) and with RFLE (range, 8 to 342 seconds; SD 91 seconds) had the widest range of time to regain consciousness in relation to patients with RTLE (range, 7 to 239 seconds; SD 48 seconds) and with LFLE (range, 6 to 280 seconds; SD 67 seconds).

The current study found that there are clinical characteristics and aspects of the epilepsy that influence the duration of the patients to be able to give an adequate response to the cognitive and behavioral testing during the postictal state. In the LTLE group these factors were having ambidextrous or right-laterality, automotor or complex-motor seizures, when patients felt obtunded after seizure, when the number of signs and symptoms during postictal state increased, when patients had aphasia and were right-handed, or had dysnomia with ambidextrous or right-laterality. In this group the duration to recover consciousness was 36.3 seconds longer than the duration of the seizure.

For the RTLE group the only factor that made the duration to recover consciousness longer was when the number of postictal signs and symptoms increased. Time to recover consciousness was shorter when patients had signs and symptoms during the seizure and opposed to the LTLE group the duration of the seizure was 13.4 seconds longer than the time to recover consciousness.

For the LFLE group patients that were awake before the seizure required more time to give a first adequate response, also if they had one or two ictal signs and symptoms or had no signs or symptoms during the postictal state. There was a negative correlation between duration of epilepsy and time to recover consciousness.

For the RFLE with the progression of the age of epilepsy onset patients required more time to recover consciousness, also when they were left-handed, felt obtunded after seizure like in LTLE, or had automotor seizures.

In relation to the seizure types, especially patients with automotor and complex-motor seizures in particular in patients with LTLE took significantly longer to recover consciousness. This correlation may be a direction of future research. Semiology of automotor and complex-motor seizures with left temporal lobe onset involves the thalamus and the basal ganglia with additional spread to the upper brainsteam structures. These structures are part of the subcortical arousal system involves in the mechanisms of losing and gaining consciousness and are typically considered to have a large involvement of cortical structures (Blumenfeld et al., 2012; Kumar & Sharma, 2018; Lüders et al., 1998). Automotor and complex-motor seizures (along with the rarer hypermotor seizures) most likely represent disinhibition of motor program networks through affection of the inhibitory networks (Blumenfeld et al., 2004; Fayerstein et al., 2020). In this current study, only patients with scalp EEG were included. Therefore, one can only speculate about the extent of the involved structures, as surface EEG will not have a fine enough spatial resolution. This could be exploited by future studies that address the recovery of consciousness in patients with invasive EEG recordings and differentiating them into the groups that have been laid out in this study.

In relation to the postictal semiology, the current study found with statistically significance that the incidence of postictal coughing in patients with temporal lobe epilepsy (31.8%) and frontal lobe epilepsy (33.3%) with right-sided lateralization can be used as a lateralizing indicator. These results are in line with the studies of Bogolioubov et al. (1994), Gil-Nagel et al. (1997), Van Ness et al. (1993) and Wennberg (2001) where they reported that temporal lobe epilepsy with right-sided lateralization had an incidence of 9 – 40%, but in their case without statistically significance. Furthermore, the first cough after the seizure in patients with RTLE can be used as an indicator of temporal lobe epilepsy with right-sided lateralization (mean 18.5 ± 18.3 seconds), followed by patients with RFLE (mean 33.7 ± 13.0 seconds). Stefan et al. (2001) suggest postictal coughing occurs in response to increased respiratory secretions and activation of central autonomic networks.

In epileptology postictal aphasia has been studied as a lateralizing sign of the dominant hemisphere in patients with temporal lobe epilepsy with focal to bilateral tonic-clonic seizures with predictive value of 80% to 100% (Fakhoury et al., 1994; Koerner & Laxer, 1988; Leutmezer et al., 2002; Noachtar & Peters, 2009), which is similar to the findings in this research, 86,4% of the patients with LTLE had aphasia. Adam et al. (2000), Ficker et al. (2001) and Ramirez et al. (2008) noted in their study that patients with right temporal lobe epilepsy and with extratemporal seizures had not postictal impairment, aphasia only appears if the seizure propagates to the dominant temporal lobe. In the present research 10.6% of the patients with RTLE and 5.3% with LFLE with focal seizures had aphasia during the postictal state because of propagation. Aphasia did change the time to recover consciousness (TRC) in the single groups by smaller amounts, but it did not change the difference between the groups for the time to recover consciousness, so this possible bias for evaluating TRC is not present in this study.

It was observed in the postictal state that during the cognitive and behavioral evaluation patients may be consistently conscious and continue to be after the FAR. On the other hand, some patients may give a FAR and then have certain amounts of time where they are confused or aphasic. So, it is important to keep asking to respond verbally and to follow motor commands until the patient give more than one adequate response to confirm regain of consciousness (Beniczky et al. 2016), this is the typical procedure at the EMU of the LMU Klinikum.

The recollection of the data for this study had to deal with the following possible limitations: (1) the first limitation was the retrospective mode of analysis; the data was selected from a database where information was already documented. In this type of investigations the researcher depends on the availability and accuracy of the medical record and the data base (Hess, 2004); (2) possibly, inconsistent testing could skew time results for patients' reaction. This possible bias was not present to a relevant extent at the EMU of the LMU University, because testing there adheres to very strict criteria, which are derived from epilepsy surgery experience and is methodically applied. These recommendations from epilepsy surgery centers have recently been published (Beniczky et al., 2016) but are based on the decade long tradition of large epilepsy surgery centers like the EMU at the LMU Klinikum. (3) Not for all semiologically different seizures, enough single seizures could be obtained to enable TRC analysis for all seizure types. This possible shortcoming could be addressed in future studies.

In conclusion, the clinically important finding of this study is that recovering of consciousness can be used as an indicator of dominant epileptic focus in temporal lobe epilepsy. Patients with temporal lobe epilepsy with left-sided lateralization required more time to be able to give a first

adequate response during the postictal state. Patients with frontal lobe epilepsy and with left-sided lateralization were the first to answer to the cognitive and behavioral testing during the postictal state.

The results obtained in this research are expected to contribute to the investigation of the process of recovering consciousness during the postictal state, to determine the clinical and the epilepsy factors that influence the process to regain of consciousness during the postictal state and to improve the cognitive and behavioral evaluation of consciousness. Also, as a lateralizing sign for the diagnostic of epilepsy for physicians who have no or limited access to neuroimaging and EEG, for selecting candidates for epilepsy surgery, and for improving quality of life of persons with epilepsy and their families.

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Affidavit

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Lara Maier, Susana

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I hereby declare, that the submitted thesis entitled

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