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EEG-network analyses in patients with genetic generalized epilepsy

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AED	Anti-Epileptic Drug
CAE	Childhood Absence Epilepsy
CohImg	Imaginary Part of Coherency
EEG	Electroencephalography
ED	Epileptic Discharge
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric acid
GGE	Genetic Generalized Epilepsy
GSWD	Generalized Spike-Wave Discharges
GTCS	Generalized Tonic-Clonic Seizure
HD-EEG	High-Definition Electroencephalography
iGTCS	Isolated Generalized Tonic-Clonic Seizures
ILAE	International League Against Epilepsy
JAE	Juvenile Absence Epilepsy
JME	Juvenile Myoclonic Epilepsy
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
SUDEP	Sudden Unexpected Death in Epilepsy
TMT	Trail Making Test
VLMT	Verbaler Lern- und Merkfähigkeitstest

1 Introduction

Epilepsy is a common, serious neurological disease with about 69 million people affected worldwide. It is characterized by an overexcitability of neurons resulting in a pathological synchronisation of neural activity and the appearance of seizures (Ngugi et al. 2011; Moshé et al. 2015). Complications of epilepsy can result in lethal outcomes, such as sudden death in epilepsy (Nashef et al. 2012). Especially in countries where medical bills are not covered by the public health system, treatment of the disease is difficult due to the potentially high cost of drugs or even the availability of medical care (Cameron et al. 2012). Moreover, patients who suffer from epilepsy are often confronted with stigma and other social problems (Quintas et al. 2012). Rates of misdiagnoses are consistently high (20%) across countries and even continents (Scheepers et al. 1998; Benbadis 2009; Oto 2017). This is significant, as the diagnosis is rarely impugned after being officially documented and thus leads to delays in diagnostics and therapy of up to 15 years (Seneviratne et al. 2014).

This thesis focuses on a specific group of epilepsy syndromes, called genetic generalized epilepsy (GGE). While it is also known under the term of idiopathic generalized epilepsy, a name by which it was commonly referred in past decades, only GGE will be used in this thesis. GGE includes various subsyndromes which present with generalized seizures and are assumed to have a genetic cause (see section 1.1.2 for further details on the subsyndromes; Jallon and Latour 2005; Scheffer et al. 2017). Its aetiology has yet not been understood completely and correct diagnosis of GGE can be difficult, leading to delays in proper treatment (Seneviratne et al. 2014). In terms of structural alterations, routine magnetic resonance imaging (MRI) usually reveals no abnormalities. But from a functional perspective, changes have been identified, for example, during resting-state. Studies using electro-encephalography (EEG) have shown distorted brain network activity in GGE patients when compared to healthy controls, indicating a possible pathophysiological feature in the disease (Chowdhury et al. 2014b; Lee and Park 2019). However, as only routine EEG devices with far fewer electrodes (usually 18) were used, spatial resolution of data is low. Consequently, the question arises as to whether similar changes can be found when using a high-definition EEG (HD-EEG) with 256 channels, as it has an improved resolution and sources can be reconstructed more thoroughly. Furthermore, neuropsychological changes have been reported in GGE patients, but it remains unclear whether these result from the pharmaceutical treatment or the disease itself (Chowdhury et al. 2014a; Moorhouse et al. 2020).

In an effort to overcome some of these limitations, this thesis will investigate possible changes in brain network activity and cognition in GGE patients during resting state. The results can shed more light on the understanding of the disease and eventually help to fill gaps in knowledge and to improve diagnostical and therapeutic procedures.

1.1 Genetic Generalized Epilepsy

GGE is an epileptic syndrome making up about 15 - 20 % of all known epilepsies with estimations ranging from 6 - 28 % (Gastaut et al. 1975; Murthy et al. 1998; Jallon and Latour 2005). The term GGE encompasses those forms of epilepsy that have a presumed genetic cause and primarily present with generalized seizures. The word idiopathic includes the Greek word "idos" meaning "self" or "own" and refers to the genetic aspect of GGE's aetiology. It also emphasizes that no other aetiology of GGE besides hereditary processes is known (Commission on Classification and Terminology of the International League Against Epilepsy 1985; Scheffer et al. 2017).

1.1.1 Definition of Epilepsy and Epileptic Seizure

According to Fisher et al. (2014), epilepsy is defined as a disease of the brain in which at least one of the following conditions apply. Firstly, the patient has experienced at least two unprovoked epileptic seizures which were not less than 24 hours apart. An epileptic seizure is described as fluctuant events of symptoms which are caused by pathologically synchronous and excessive neuronal brain activity (Fisher et al. 2005). Secondly, the patient has experienced one unprovoked seizure in combination with a high probability (at least 60 %) of suffering another within the next ten years. An increased probability for another seizure could be assumed from findings of typical epileptic patterns in imaging, such as EEG or MRI abnormalities. The last condition is the diagnosis of an epileptic syndrome (Fisher et al. 2005).

In general, epilepsies can be categorised according to the type of seizures which have occurred. These can be focal, generalized or unknown (Fisher et al. 2017). In focal epilepsies seizures originate from one or more specific areas in the cortex of one hemisphere. In about 60 % of the cases this area is in the temporal lobe, followed by frontal areas. Seizure onset in parietal or occipital lobes is rare (Smithson and Walker 2012). Focal seizures can further be divided into seizures with retained or impaired awareness. If awareness is not compromised, patients are still aware of themselves and of the environment around them during the event (Fisher et al. 2017). Depending on the onset location, symptoms of what are referred

to as focal aware seizures can be auditory or olfactory hallucinations, illusions or complex motor posturing (Smithson and Walker 2012). While focal impaired awareness seizures can start as such, they are usually accompanied by changes in consciousness. This can become manifest in automatisms such as lip smacking, swallowing, fiddling with the hands or, especially in frontal lobe seizures, more intricate movements, for example running, pushing away, or taking an odd posture. Usually, such a seizure lasts less than a minute and patients themselves are amnesic towards the seizure and usually are confused afterwards (Smithson and Walker 2012). Whenever a seizure starts focally but epileptic discharges spread across both hemispheres, it is called focal to bilateral tonic-clonic and can result in convulsions (Smithson and Walker 2012).

GGE, however, belongs to the group of what are referred to as generalized epilepsies. In these, seizures are characterized by epileptic discharges initially across both hemispheres (Smithson and Walker 2012).

1.1.2 Clinical Presentation of GGE

Symptoms of GGE can be diverse as clinical manifestation depends on various factors such as the initial location of the respective seizure type, brain-maturity or medication (Fisher et al. 2005). They can, for instance, result in a change of motor or sensor function or have an effect on consciousness, cognition and emotional state (Fisher et al. 2005).

Three common seizure types are often found in GGE: absences, myoclonic seizures, and generalized tonic-clonic seizures (GTCS). With 47 %, absences are the least frequent type in GGE, followed by myoclonic seizures (56 %) and GTCS (80 %; Asadi-Pooya et al. 2013). Percentages do not total 100 % because more than one may be exhibited in any individual.

Absences are characterized by a sudden loss of consciousness during which patients show symptoms such as staring, motor arrest or head-flopping. These seizures only last a few seconds, can happen multiple times per day and may even be unrecognized. Patients recover immediately afterwards and experience no post-ictal phase. In EEG 5 - 20 ms discharges of spikes and waves can be observed (Smithson and Walker 2012; Mullen and Berkovic 2018; see section 1.1.5 for further information on typical epileptic discharges).

Myoclonic seizures appear as sudden muscular jerks. These might involve the whole body or only parts of it such as the upper limbs. Respective EEG is characterized by spike or polyspike-wave discharges (Smithson and Walker 2012; Mullen and Berkovic 2018).

The most common subtype is the GTCS in which patients initially often show tonic (i.e., stiff) posture, sometimes accompanied by a characteristic yell. Afterwards, they will fall and possibly bite their tongue once their jaw cramps. In the following seconds clonic movements start, their focus often being on the upper limbs. These movements can be described as regular jerks which are coordinated and ultimately slow down and come to a halt. At this point incontinence can occur. Overall, GTCSs usually last no longer than two minutes. Patients experience a postictal period which is characterized by confusion and fatigue and lasts for up to 20 minutes. However, the effects of the seizure often spread across a longer period of time appearing as lethargy, muscle ache, or injuries acquired during seizure, for example tongue bites (Smithson and Walker 2012; Mullen and Berkovic 2018).

According to the International League Against Epilepsy (ILAE), the different types of clinical presentation can be assigned to four epileptic syndromes which make up the spectrum of GGE: Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME) and isolated generalized tonic-clonic seizures (iGTCS; Scheffer et al. 2017).

CAE makes up about 1 - 10 % of GGE syndromes (Berg et al. 1999; Asadi-Pooya et al. 2013). Patients start to develop seizures at age four to eight and are, in majority, female. Usually, the seizures become manifest in absences, however, next to the typical absences described previously, also atypical ones can occur. These are characterized by tonic or atonic patterns more often found in children with mental retardation (Holmes et al. 1987; Mullen and Berkovic 2018). Atonic means a rapid loss of body tone which can eventually result in a fall (Smithson and Walker 2012). A hallmark of CAE is the high frequency of seizures. They often take place multiple, sometimes up to a 100, times per day (Mullen and Berkovic 2018). As a result, for instance, patients' school performance decreases (Jackson et al. 2013). In EEG spike-wave discharges at 3 - 4 Hz can be observed. Interestingly, most patients can become seizure-free using anti-epileptic drugs (AED). However, a minority additionally develops GTCSs during adulthood (Smithson and Walker 2012).

While there is a great overlap in terms of seizure type with the previous form, JAE occurs later, with initial seizures at age 10 - 17 (Tondelli et al. 2016) making up about 10 - 15 % of GGE (Jallon et al. 2001; Asadi-Pooya et al. 2013). Absences happen at a lower frequency than in CAE. However, GTCSs occur more often, and sometimes even myoclonic jerks take place. While the usage of AEDs can be successful, JAE tends to endure into adulthood (Smithson and Walker 2012).

JME presents within a wider age range of 8 - 26 years and with typically myoclonic seizures not lasting longer than 30 minutes. In addition, GTCSs occur in most and absences in a third of JME patients (Smithson and Walker 2012). JME patients often do not attend a doctor for years until additional convulsive or absence seizures arise (Sullivan and Dlugos 2004). Frequency of JME varies immensely with estimates of between 20 - 40 % of all GGEs (Jallon and Latour 2005; Asadi-Pooya et al. 2013). The treatment of JME is possible, still, the disease often accompanies the patients throughout their lifespan (Smithson and Walker 2012).

Prevalence of iGTCS is difficult to estimate, as many syndromes additionally present with such seizures (Jallon and Latour 2005). According to a study on an Irish cohort, iGTCS occurs in 21 - 48 % of GGE patients (Mullins et al. 2007; Asadi-Pooya et al. 2013). This subsyndrome becomes manifest at age 6 - 24 and the majority of GTCSs occurs within the first two hours after waking up, independent of time of day (Sullivan and Dlugos 2004).

When an epileptic seizure lasts longer than, or repeatedly occurs without recovery for, 30 minutes, it is called status epilepticus (SE; Shorvon 2006). It is a neurological emergency that, if not treated immediately, can lead to brain oedema as well as central circulation and heart failure (Hacke et al. 2010). The mortality rate of SE is estimated at 20 % (Logroscino et al. 2005). Chronic epilepsy, of which GGE is an example, and low AED usage have been reported to be the most frequent causes of SE (Betjemann and Lowenstein 2015). The severest complication of GGE is probably the sudden unexpected death in epilepsy (SUDEP). It is defined as a "sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause for death" (Nashef et al. 2012, p. 6). SUDEP is assumed to be the main cause of increased mortality reported for epilepsy patients and the incidence in chronic epilepsy is high (2-5/1000; Tomson et al. 2008). Besides a young age of onset (< 16 years) or a long duration of the disease, insufficient control of GTCSs is the most important risk factor for SUDEP (Hesdorffer et al. 2012a).

Besides seizures, GGE can be accompanied by other diseases. About 20 % of GGE patients have a psychiatric condition as a comorbidity. The most common are mood (46 %) and anxiety disorders (26 %; Akanuma et al. 2008; Gesche et al. 2021). This trend can be observed in all GGE subsyndromes and seizure types. Moreover, control of seizures was significantly better in patients without, than in those with, psychiatric comorbidity (Akanuma et al. 2008). The reasons for this association are enigmatic. Possible influence of polypharmacy, side effects of AEDs, or psychosocial factors are under consideration. GGE patients, for instance,

have a higher probability of being unemployed, a lower income and, in general, a lower social status when compared to healthy controls (Akanuma et al. 2008; Gesche et al. 2021). Vice versa, psychiatric disorders may enforce a lack of compliance and may interfere with patients' capability to avoid certain seizure risk situations such as sleep deprivation (Akanuma et al. 2008). GGE patients tend to present with personality traits such as emotional lability or lack of self-control. Such features could increase their risk of developing mental and behavioural issues (Janz 2011). Furthermore, Hesdorffer et al. (2012b) even suggest a common underlying pathophysiological mechanism lowering both the threshold for development of seizures and for psychiatric disorders. In addition to psychiatric, somatic comorbidities have also been identified. Examples include dementia, migraine, strokes, or even cardiac and respiratory diseases. This increase has been found in epilepsy in general, but not with respect to a specific subsyndrome (Gaitatzis et al. 2012).

1.1.3 Aetiology

The aetiology of epilepsy itself is diverse but, according to the ILAE, can be described by structural, genetic, infectious, immune, or unknown factors (Scheffer et al. 2017). Basically, any process able to induce structural or functional disturbances in the brain's physiology can lead to the formation of seizures (Vezzani et al. 2016). It should be noted that the aforementioned categories are not mutually exclusive. In fact, often multiple factors contribute to the development of the disease (Balestrini et al. 2021). In about 30 % of patients however, aetiology remains unknown. This high number illustrates the need for a better understanding of the pathological principles underlying epilepsy (Balestrini et al. 2021).

It is presumed that the main cause for GGE lies in genetic predispositions (Sullivan and Dlugos 2004). While some genes have been identified, the genetic aetiology is complex (Helbig 2015). Twin studies showed an enlarged concordance for GGE syndromes in monozygotic (80 %) when compared to dizygotic twins (26 %). This enforces the assumption of a mainly genetic causative model (Berkovic et al. 1998; Kjeldsen et al. 2001; Helbig 2015). Furthermore, a population-based study showed that the risk for developing epilepsy was increased six-fold in first degree-relatives of GGE-patients, almost twice as high when comparing it to the risk for relatives of all epilepsies combined (Peljto et al. 2014). Some genes have been identified as playing a role in GGE. The sodium channel alpha 1 (SCN1A) and beta 1 (SCN1B), for instance, are genes coding for respective subunits of a voltage-gated sodium channel in the brain. Both have been found to be altered in GGE patients (Wallace et al. 1998; Wallace et al. 2001a; Helbig 2015). Moreover, mutations of a gene coding for a

subunit of a gamma-Aminobutyric acid- (GABA) receptor in the brain were the main phenotype in respective families with CAE (Wallace et al. 2001b). Also, Chen et al. (2003) found that the mutation of a calcium channel, necessary for the thalamocortical circuitry, can increase likelihood for development of GGE. Interestingly, while responsible mutations can be inherited, some can also be spontaneously acquired (Claes et al. 2001; Scheffer et al. 2017). The copy number variants, for instance, are duplications or deletions of genomic substance of at least a thousand base pairs and are thought to occur de novo in unrelated patients (Joober and Boksa 2008; Mefford and Eichler 2009; Zarrei et al. 2015). A large cohort analysis revealed such a microdeletion at 15q13.3 in 1 % of GGE patients. In line with this, there was practically no evidence of deletions found in controls (Dibbens et al. 2009; Helbig et al. 2009). About 2 - 3 % of genetic alterations responsible for GGE are assumed to occur due to such microdeletions (Helbig 2015). Up to now, about 16 gene loci have been identified as being involved in epilepsy syndromes. The majority of these are found in GGE and explain about a third of variance in the disease spectrum (The International League Against Epilepsy Consortium on Complex Epilepsies 2018)

1.1.4 Pathophysiology

An epileptic seizure is the result of a pathologically synchronous neuronal activity disturbing physiological neuronal communication in the brain (Moshé et al. 2015). This increase of neuronal excitability can be found in every epileptic syndrome (Engelborghs et al. 2000). Both inhibitory and excitatory neurons are involved and cause a variety of neuronal regions to be affected including brain networks leading to dysfunctions (for example learning disabilities; Bertram 2013; Galanopoulou and Moshé 2014; Moshé et al. 2015).

While the pathophysiological processes of epilepsy taking place are not fully understood, one focus has been on the ion channels of neurons (Engelborghs et al. 2000; Bertram 2013). Changes in voltage-gated sodium (Na+) channels of the brain, for instance, have been found in patients with epilepsy. The main task of these channels is to initiate and disseminate action potentials (Alexander et al. 2015; Oyrer et al. 2018). A dysfunction of them, as found in patients with severe myoclonic seizures, causes a reduction of sodium current in inhibitory neurons which could explain hyperexcitability (Yu et al. 2006). Potassium channels have also been linked to the development of epilepsy. Biervert (1998) was able to show that a loss-of-function mutation in a gene coding for potassium channels, responsible for repolarization of membrane potential, would eventually result in hyperexcitability and thus seizures. A calcium channel important for neurotransmitter release was found to be involved. Its dysfunction led

to a reduced discharge of excitatory neurotransmitters in cortico-thalamic synapses and sufficiently generated generalized seizures. While a following imbalance of neuronal excitation and inhibition is assumed, it is not completely understood how this pattern contributes to an increased network excitability (Bomben et al. 2016).

In terms of the influence of neurotransmitters, various results were reported. The amino acid transmitter GABA, for instance, a neurotransmitter essential for inhibition of neuronal processes, was found to enforce seizure probability when being hindered. The other way around, it had an anti-epileptic effect when it was promoted (Treiman 2001). Furthermore, the number of GABA-ergic somata was reduced in epileptic foci of monkeys (Ribak et al. 1986). Another neurotransmitter of interest is glutamate which plays an essential role in epileptic pathophysiology as the activation of its receptors enforces epileptic seizures (Engelborghs et al. 2000). In line with this notion, an up-regulation of glutamate receptors was discovered in patients with temporal lobe epilepsy (Pitsch et al. 2007).

1.1.5 Diagnostics

Correctly diagnosing epilepsy is a complex procedure (Berg et al. 2010). First, a thorough history of the patient should be taken. This can be difficult as patients sometimes do not remember their seizures and gaining appropriate information may thus have to rely on witness reports. In general, questions should enlighten symptoms such as sudden fall, involuntary muscle jerks, urinary incontinence, or tongue bites accompanied by loss of consciousness or phases of impaired awareness and confusing behavioural actions (Smithson and Walker 2012). Also pre-existing conditions, for example a tumour, and family history should be explored (Moshé et al. 2015).

Clinical neuroimaging, such as MRI, should be conducted to rule out or identify possible structural pathologies as a cause for the seizures. Routine blood samples, testing for plasma glucose and electrolytes as well as seizure description or age of onset can further be examined. To take into account cardiac issues, a 12-lead electrocardiography (ECG) is also necessary (Moshé et al. 2015).

The most important tool for the diagnosis of GGE, however, is the EEG. It is a method by which bio-electrical activity of neurons in the brain is obtained where electrodes are positioned on the patient's head. A routine EEG recording usually lasts up to 30 minutes, is mostly painless, is not invasive and can be repeated as often as desired (for further details on EEG, see section 1.3). Using EEG, epileptic discharges (ED) can be observed and thus help to characterize the epileptic syndrome. Therefore, it is helpful to catch a seizure on EEG.

This can be done by provoking a patient during recording, for instance, by hyperventilation, photo-stimulation, or sleep deprivation. The latter is usually performed during a 24-hour EEG and video recording in an inpatient setting. EDs occurring during a seizure are called ictal discharges. Correspondingly, EDs observed outside of a seizure are described as interictal (Hacke et al. 2010). Interictal EDs last only a few seconds and occur in bursts or solely. Ictal discharges, however, are repetitive, show a sudden onset and ending, and endure for several seconds (Kane et al. 2017).

The most typical interictal features of GGE are symmetrical generalized spike-wave-discharges (GSWD), occurring bilaterally and synchronously (Seneviratne et al. 2017b). A more detailed approach of the GSWD identified an initial negative spike with a low amplitude (25-50 uV) lasting for about 10 ms, followed by a 100-150 ms lasting positive transient. Afterwards, a second negative spike occurs for 30 - 60 ms and is usually larger in amplitude than the first spike. This is followed by the wave of negative polarity which spreads across 150 - 200 ms (s. Figure 1; Weir 1965). Interestingly, spike one is seen less frequently than the second spike (Blume and Lemieux 1988). The strongest amplitude of GSWD was observed over frontocentral regions (Seneviratne et al. 2016).

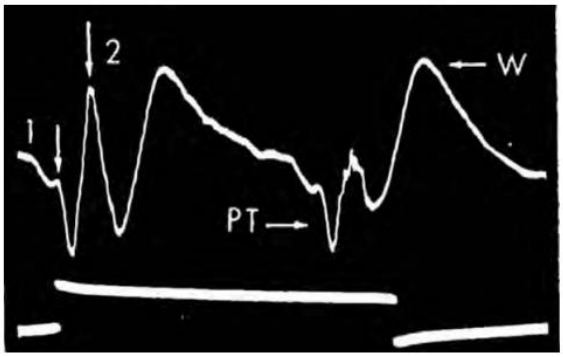

Figure 1: Recording of spike-wave-complexes. Data were collected during a seizure in a 12-year-old child using an oscilloscope. 1st white arrow = spike 1; 2nd white arrow = spike 2; PT = positive transient; W = wave. Electrode combination is F4-A2 (Weir 1965). With kind permission from Elsevier.

GSWDs can occur as single spike waves, polyspike-waves, or spike-wave-complexes arising at 3 - 4 Hz pace (s. Figure 2; Hacke et al. 2010). In CAE, patients show GSWDs at 3 Hz and in over 90 % parts of GSWDs occur especially during drowsiness or even sleep (Commission on Classification and Terminology of the International League 1989; Sadleir et al. 2009). For JAE, GSWD patterns in EEG are more fragmented or appear as polyspikes, again especially during drowsiness and sleep (Sadleir et al. 2009). Interictal EEG in JME patients shows spikes and polyspike-waves at a pace of 3 - 6 Hz (Panayiotopoulos 2005). With an average spike-wave frequency of 3.6 Hz iGTCS patients present with GSWDs including polyspikes

and polyspike-waves. However, they appear less frequently than in CAE, JAE or JME (Seneviratne et al. 2017a).

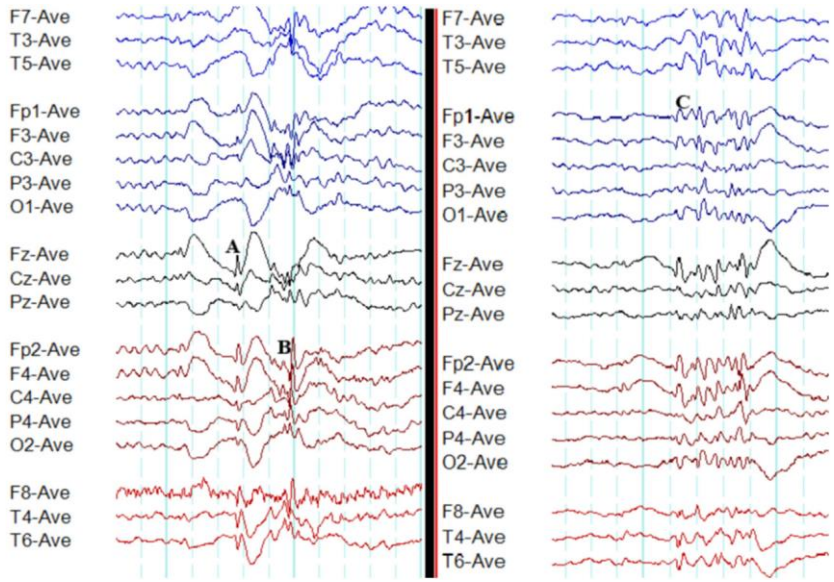

Figure 2: Examples of typical epileptiform discharges in genetic generalized epilepsy. A = spike-wave discharges; B = polyspike-wave-discharges; C = polyspikes (Seneviratne et al. 2017b). With kind permission from Frontiers Media SA.

Ictal EEGs also come with characteristic patterns depending on the subsyndrome. Myoclonic seizures, for instance, present with a generalized polyspike paradigm at 10 - 16 Hz and with the maximum being localized over frontocentral regions. This pattern may be antedated by 2 - 5 Hz GSWDs and, in some cases, slow waves (1 - 3 Hz) following afterwards (Delgado-Escueta and Enrile-Bacsal 1984). Typical absence seizures look a bit different with GSWDs at 2.5 - 4 Hz. However, the discharges' maximum is again found over frontocentral areas (Drury and Henry 1993). Concerning iGTCS, the EEG signal is often masked by severe muscle and movement artefacts during seizure. The beginning of the seizure is characterized by generalized polyspike-wave bursts occurring at 20 - 40 Hz for a few seconds. While the amplitude decreases, the tonic phase of the seizure starts. Afterwards, a generalized rhythmic activity (10 - 20 Hz) develops with increasing amplitude on the one hand and decreasing frequency on the other. Once the frequency decreases down to 4 Hz, recurrent polyspike-wave patterns appear. At the same time clonic jerks emerge. As soon as the seizure terminates, the background EEG rhythm slowly changes from delta to theta and eventually alpha. The beginning of a tonic-clonic-seizure can be seen in Figure 3 (for further details on respective frequency bands, see section 1.3; Hrachovy and Frost 2006).

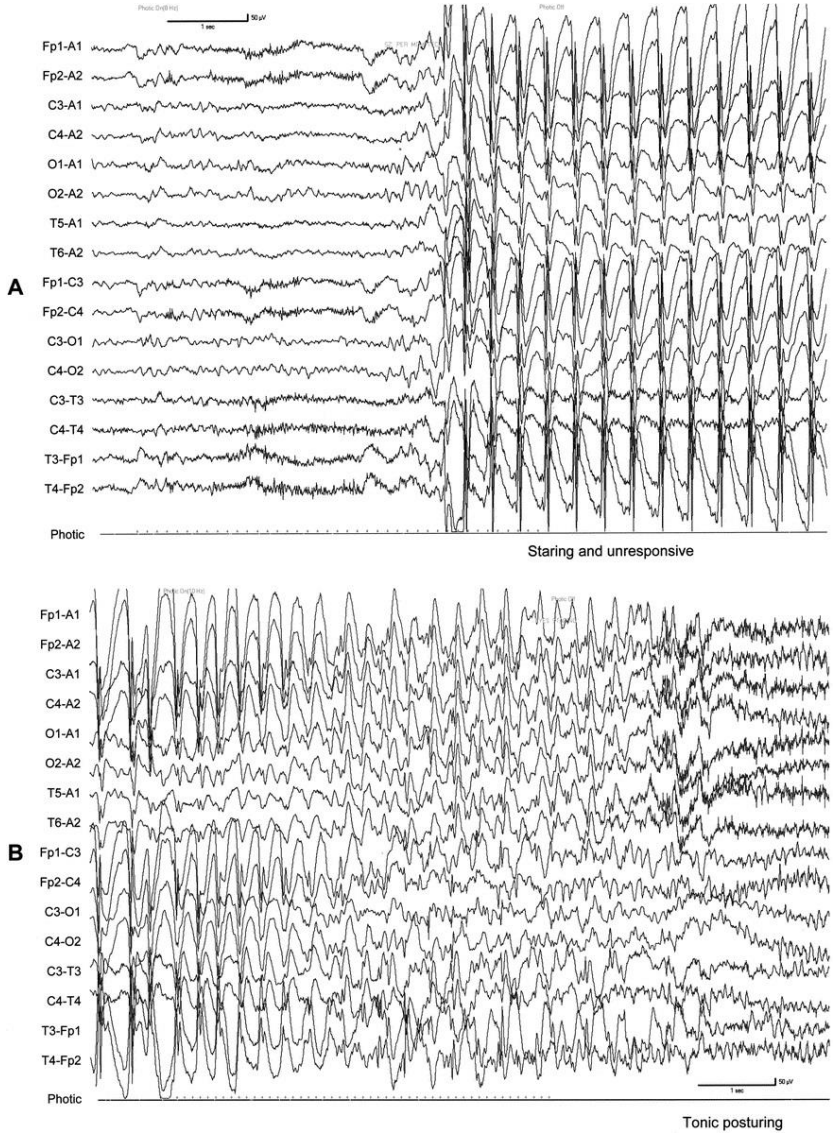

Figure 3: Electroencephalography of a generalized-tonic-clonic seizure. This was observed in a nine-year old patient after initial photo-stimulation. **A**: Note the burst of 3 Hz spike-wave patterns after photic stimulation during which the patient showed loss of consciousness and staring. **B**: With the beginning of the tonic phase these bursts change into a generalized alpha frequency (Hrachovy and Frost 2006). With kind permission from Wolters Kluver Health, Inc..

Given its complex diagnosis, many diseases are mistaken as epilepsies. Rates of misdiagnoses are estimated at 20 % (Oto 2017). This is especially the case for important differential diagnoses such as convulsive cardiac syncope or psychogenic non-epileptic attacks. In a drastic example, 21 % of patients diagnosed with epilepsy actually had heart problems (Petkar et al. 2012). Eighty percent of the cases with misdiagnosis were seizure-free and asymptomatic after proper treatment of their cardiac issues. Misdiagnoses also happen within the epileptic subsyndromes. For example, GGE can sometimes present with EEG features typical of focal

epilepsy and thus be mistaken for it. This error can occur the other way round, as some focal epilepsies, such as frontal lobe epilepsy, present with secondary generalized seizures. These seizures show bifrontal epileptiform discharges in EEG recordings which look similar to GSWDs (Seneviratne et al. 2017b). It is of interest that spike-wave patterns can also be found in healthy subjects. One example is the phantom spike-wave. While it too is generalized and can appear at 6 Hz bursts, it only lasts up to 4 s, only develops during drowsiness and disappears in sleep (Klass and Westmoreland 1985). Such patterns are benign and have no clinical significance (Seneviratne et al. 2017b). Misdiagnosis can of course have a tremendous effect on therapy success including a possible worsening of seizures. Consequently, it can result in a delay of correct diagnosis of 6 - 15 years (Seneviratne et al. 2014). Yet, as can be seen from the aforementioned issues in the diagnostics of epilepsy, there continues to be a lack of knowledge of the disease which calls out for more research to better understand the underlying mechanisms and improve sensitivity and specificity of diagnostic tools (Seneviratne et al. 2017b).

1.1.6 Treatment

AEDs are the main component of epilepsy treatment. The basic principle of most of AEDs is the interaction with ion channels (e. g. sodium or calcium channels) and neurotransmitters resulting in reduction of excitability at the neuron's membrane (Engelborghs et al. 2000). Many AEDs are used in treating epilepsy and reviewing the complexity of each is not the goal of this thesis. As a result, this section will only give a short overview of commonly used drugs. For treating absences Ethosuximide, Lamotrigine or Valproic acid, amongst others, can be prescribed. While the latter reinforces the activity of GABA-ergic inhibitory neurons, the other two hinder ion channel function (e. g. sodium channels) and result in reduction of the neurotransmitter glutamate. When myoclonic seizures must be controlled valproic acid can be used as well. As an alternative, Topiramate can be applied, an AED which reduces glutamate levels. Next to these two, GTCSs can be treated with Lamotrigine or Carbamazepine, a sodium-channel-inhibitor (Duncan et al. 2006).

No AED exists that works for all epileptic disorders and response rates vary depending on the subsyndrome (Moshé et al. 2015). However, by using AEDs, seizure freedom can be achieved in 70 % of patients with epilepsy (Duncan et al. 2006). In general, a mono-therapeutic approach should be the starting point, as about half of the patients with epilepsy respond to their first AED (Hacke et al. 2010). If seizures persist, a change of medication, such as adding another or exchanging AEDs, can lead to seizure-freedom in another 15 % of

patients. However, if a patient's epilepsy is unresponsive to at least two AEDs, chances of seizure-freedom are reduced to only 5 % (Brodie et al. 2012). Hence, about a third of patients are estimated to present with drug-resistant epilepsy in which seizures cannot be controlled (Kwan 2004). This is a significant problem as seizure freedom is the principal factor affecting quality of life in epilepsy patients (Silva et al. 2019).

As reviewed in the previous paragraphs and section 1.1.5, gaps in diagnosis and treatment of epilepsy, and GGE in particular, still exist. These gaps underscore the fact that the pathophysiological processes of GGE are not yet completely understood. It is therefore necessary to further investigate mechanisms underlying the disease and in so doing enhance the understanding of GGE (Moshé et al. 2015).

1.2 Functional Changes of GGE in EEG/MEG

This section starts with a brief overview on structural abnormalities found in GGE to present a more thorough picture of neuronal changes observed in this disease. Usually, routine cranial MRI images of these patients are unremarkable, although some studies reported structural changes. Focke et al. (2014), for instance, found alterations in white matter of the corpus callosum, superior and longitudinal fasciculus and supplementary motor areas using diffusion tensor imaging. Other studies described structural differences in thalamocortical networks and the cerebellum when compared to healthy controls (Deppe et al. 2008; Li et al. 2010). Analysis of grey matter volume revealed consistent alterations in fronto-central regions for GGE patients, especially those with JME (Betting et al. 2006; Bernhardt et al. 2009; Huang et al. 2011). It is of interest that in one study grey matter volume was decreased for JME but increased for absence patients (Betting et al. 2006). Thus, such changes could imply another pattern to differentiate GGE subsyndromes from one another (Elshahabi et al. 2015). Next to structural abnormalities, functional alterations have also been identified, a discussion of which follows.

While the tools with which results were acquired vary, this thesis focuses on functional changes of GGE patients in EEG using, in the main, two parameters: power and functional connectivity (FC). Power can be described as the squared amplitude of a signal (Lehmann and Michel 1989). In EEG this parameter is often extracted from each of the frequency bands (delta, theta, alpha, beta, and gamma) as a reference for their respective signal strength. Power is of interest when exploring GGE since it reflects neuronal activity and, as stated in section 1.1.4, an underlying mechanism of GGE, namely the hypersynchronous activity of neurons (Clemens et al. 2000). Pegg et al. (2020), for instance, found a significantly higher

power of EEG-signal at theta, beta, and gamma bands in GGE patients when compared to healthy controls.

FC is a common metric to observe functional dynamics of neuronal groups. It is defined as the temporal correlation between two locally separated neurophysiological events. In short, it represents the coactivation of neuronal populations in different areas of the brain (Friston et al. 1993). One way to observe FC is by exploring it during resting-state. Subjects are usually asked to lie down quietly and to think about nothing specific but not to fall asleep (Fox and Greicius 2010). FC has been investigated, for instance, when looking at GSWDs. At present, where and how GWSDs originate is only partly understood. Some regions have been identified as playing a larger role in its development including the thalamus, and the posterior cingulate cortex as well as frontal regions. However, whether these regions initiate GSWDs or whether they are simply activated by them remains unknown (Aghakhani 2004; Hamandi et al. 2006). Current research suggests that prefrontal regions and sensorimotor networks play key roles in initiating GSWDs (Tangwiriyasakul et al. 2018). Furthermore, the question arises as to whether there are functional neuronal networks comprised in GGE. Indeed, FC of thalamo-cortical connections was observed to be altered during GSWD in GGE patients using combined EEG and functional MRI (fMRI) techniques (Blumenfeld 2005; Gotman et al. 2005). This pattern was confirmed by magnetoencephalographic (MEG) analyses emphasizing the importance of the thalamocortical pathways in GGE (Stefan et al. 2009).

While the mentioned studies have focused on intervals showing GSWDs, another approach is to look at the GSWD-free periods, as the latter is assumed to show normal brain activity. Moeller et al. (2011) compared GSWD and GSWD-free intervals using simultaneous EEG and fMRI. While thalamo-cortical connectivity was altered during GSWDs, it did not significantly differ from controls during GSWD-free intervals. This observation implies a potential difference in neuronal network involvement between those two phases (Moeller et al. 2011). Several EEG and MEG studies have approached the topic by focussing on such GSWD-free intervals. Their findings, though, are ambivalent. In one study FC was found to be decreased in low (1 - 6 Hz) and increased in higher frequencies (Clemens et al. 2011). Chavez et al. (2010) also found an increase in FC but only in alpha frequency band (5 - 14 Hz) whereas Chowdhury and colleagues (2014b) reported it only for the lower alpha band (6 - 9 Hz). Niso et al. (2015), on the other hand, identified increased FC in all frequency bands except alpha.

Most of the studies described in the previous paragraph used a sensor level approach to calculate FC. This means that connectivity was measured between the EEG/MEG

electrodes directly. This, however, can hinder links between anatomical neuronal locations and found connectivity due to a problem called field spread or volume conduction (for further information on this matter, see section 1.3). This approach affects connectivity estimates at the sensor level and leads to many electrodes showing a correlated activity and hence connectivity where there is none of the underlying neuronal sources. One solution to this issue is to base interactions on reconstruction of respective neural sources using individual MRI images of the subjects' brains or simply an MRI template. An example is to create a surface head model where each electrode in a group is weighted differently. The weighted sum of all electrodes will then serve as an estimate of neuronal activity at a certain location in the brain (Michel et al. 2004). By doing so, one is faced with what is referred to as the inverse problem: by EEG/MEG a three-dimensional reality is projected to two dimensions; thus it is impossible to securely locate the signals' origin by having electrodes record it from the scalp (Olejniczak 2006). While there is no perfect solution for this issue, it can be addressed by solving the forward problem which can be seen as the opposite of the inverse problem: the estimation of electric potential of electrodes from a known source in the brain. If the forward problem is solved, reconstruction of electronic source distribution will be possible (Patoner 2021). Eventually, volume conduction effects can be reduced with this procedure (Haufe et al. 2013). It is important to note that even by using such a source-based analysis, the problem of volume conduction can never be eliminated completely (Schoffelen and Gross 2009).

With such a source-based analysis Elshahabi et al. (2015) found an increase in FC and power for GGE patients compared to healthy controls using MEG. These patterns were emphasized over the mesio-frontal and temporal cortex as well as the motor network in delta, theta and beta frequency bands for power and beta frequency bands for connectivity respectively (Elshahabi et al. 2015). Similarly, Li Hegner et al. (2018) also found increased FC for GGE patients in the theta, alpha and beta frequency bands. However, both studies had an overlap in GGE patients. A more recent study by Stier and colleagues (2021) with a completely new sample of larger size than the previously mentioned investigations also reported widespread increases in FC and power in GGE patients. Comparison of FC between GGE and controls revealed an increase in all frequency bands except delta with strongest differences observed in left-hemispheric temporal, frontal, central, and parietal regions. Concerning power, an increase for GGE was observed in all frequency bands with an emphasis on temporal and occipital-parietal areas (Stier et al. 2021). In addition, the authors also analysed the influence of certain clinical variables on MEG oscillations. They compared patients who had shown GSWDs in the initial MEG recording to those who had not. Although GSWDs had been

excluded in the MEG analysis, results implied an increase of FC and power for patients with GSWDs. These were found in delta and beta-frequency bands. Moreover, they investigated the effect of medication on EEG signal and reported a decreased FC for those patients who took two or more AEDs compared to those who took fewer AEDs at the time of investigation. Patients were also compared regarding the time since their last seizure. No significant difference in FC or power was found between patients who had experienced a seizure within 12 months prior to investigation and those who had not (Stier et al. 2021).

While all three previously mentioned studies have used a source-analysis approach, they used MEG to explore functional changes in GGE patients. The common pitfall of this approach lies in the limitations of MEG as a method, which is more sensitive to tangential sources than to radial sources in the brain (Baillet et al. 2001). It is therefore important to investigate issues with EEG, which is sensitive to both radial and tangential sources in the brain (Baillet et al. 2001). This is one of the principal goals of this thesis. To improve and test validity of results, EEG data from the same patients which were observed by Stier et al. (2021) are used for the analyses. By keeping the data base constant, a clear methods benchmark can be obtained. Testing whether and how much results of both approaches overlap is another principal aim of this thesis.

1.3 Physiological Principles of EEG

To study FC and power EEG recordings were used. However, to understand the potential results, it is important to clarify the basic physiological principles of EEG. It is a method to measure electrical activity at sensor level over time (Berger 1929). Therefore, electrodes are placed on the participant's scalp. The current measured by these electrodes is generated by the synchronized postsynaptic activity in groups of cortical neurons; pyramidal cells to be more specific (Jackson and Bolger 2014). Such cells are located at cortical layer III, V and VI and the current created varies between 10 - 100 mV (Kaur and Kaur 2015). Both inhibitory and excitatory postsynaptic potentials (IPSP; EPSP) of the neuron's cell membrane influence the signal (Olejniczak 2006). If, as an example, a group of neurons is depolarized, it results in an extracellular current at their dendrites that is more negative than anywhere else at the neuron's membrane. Since this circumstance creates an area with a more positive and another with a more negative charge around the neuron, a dipole is created. This process is inverted with polarizing current creating a more positive charge at the neuron's dendrites. However, the strength of a single neuron's dipole is not sufficient to be measured outside on the brain's scalp by EEG. Interestingly, it is estimated that an activity of at least 108 neurons spreading

over an area of 6 cm^2 is necessary to create a visible scalp EEG signal (Olejniczak 2006). EEG electrodes can only detect the sum of dipoles from several neurons close to them, both positive and negative in charge (Olejniczak 2006). To detect a dipole, electrodes need to be closer to either the positive or negative side. If they are located in the middle, they will measure a net neutral (Jackson and Bolger 2014). As a result, only two basic dipoles can be measured, tangential and radial dipoles. While tangential dipoles are located parallel to the brain's surface, radial dipoles are positioned perpendicular to it (Whittingstall et al. 2003). Dipoles create different signal polarities with either a more positive or more negative deflection depending on the location of the electrode on the scalp (Jackson and Bolger 2014). As the electrodes quantify the sum of both positive and negative ends of the dipoles, it is important to note that neurons must therefore be grouped in a parallel manner and synchronously active to acquire a nonzero EEG signal (Jackson and Bolger 2014). By doing so, their signals are additive and take form in a more intense oscillation. This synchronous activity is necessary in order to create a large enough signal to be captured by EEG electrodes (Jackson and Bolger 2014). However, it needs to be emphasized that the signal recorded at the electrode cannot differentiate between excitatory or inhibitory neural activity. If, for instance, an EPSP arrives at the postsynaptic dendrites and the dendrites are located closer to the electrode than the neuron's soma itself, depolarization of dendrites will lead to a negative extracellular charge and thus a negative EEG-signal.

It is assumed that the synchronism underlying neuronal activity is controlled by thalamocortical and cortico-cortical connections (Buzsáki 2006). While the main origin of the signal itself is thought to arise from cortical gyri and sulci, a strong dipole from deeper parts of the brain can still affect the EEG signal. Nevertheless, it is not understood in what ways these sources might interfere with more shallow ones (Anastassiou et al. 2011; Jackson and Bolger 2014). As the neural activity cycles, the signal recorded by the electrodes on the scalp rapidly switches between positive and negative charge. The rate at which these cycles occur is represented by the frequency of the signal. Most scalp EEGs investigate frequencies between 0.1 Hz and 80 Hz. To date, discovered frequency bands have been divided arbitrarily into the following: delta (1 - 4 Hz), theta (4 - 8 Hz), alpha (8 - 12 Hz), beta (12 - 30 Hz) and gamma (>30 Hz; Buzsáki 2006). However, the gamma is difficult to analyse due to its alterations by skull, muscle and ocular artefacts and hence is often left out (Jackson and Bolger 2014).

A dipole in the brain will influence several electrodes in a certain range of locations around it and not just the one directly above. As a result, one electrode records activity of several

neuronal sources. This is called the volume conduction problem (Jackson and Bolger 2014; Bastos and Schoffelen 2016). It can lead to severe misinterpretations. As an example, if signals of two electrodes correlate highly with each other, one can assume a potential connection between two separate underlying neuronal sources. However, this pattern could arise from two electrodes simply recording the same source but just from two different positions (Bastos and Schoffelen 2016). Volume conduction is enforced in non-invasive EEG especially, because the signal of the neural sources must cover a large distance from source to electrode. Furthermore, travelling through the scalp tissues and skull blurs the electrical distribution on the scalp and further alters the recorded signal (Burle et al. 2015).

1.4 Neuropsychological Changes in GGE

As the underlying mechanism of epilepsy in general is believed to be a hypersynchronous activation of neuronal populations, one could assume that diseases of the epileptic spectrum also result in changes to cognitive performance. Indeed, studies do show dysfunctions of cognitive domains in patients with epilepsy. These include impairments in memory, attention, problem-solving, learning, and perception (Motamedi and Meador 2003).

Cognition in GGE is reported to be within normal range, but slightly worse than the general population on average (Jeong et al. 2011; Loughman et al. 2014). According to Chowdhury et al. (2014b) these changes concern impairments in attention, working memory, letter fluency, and general IQ. Some studies reported specific cognitive profiles for GGE-subsyndromes, for example specifically impaired executive functions in patients with JME (Wandschneider et al. 2010). However, a meta-analysis of cognitive changes in GGE did not reveal a distinct profile of cognition for any of the subsyndromes. In addition, it identified common impairments in processing speed, working memory, and memory retrieval over all subsyndromes (Loughman et al. 2014).

Problems in cognition are influenced by several clinical factors, for example AED-treatment (Jokeit and Ebner 1999; Drane and Meador 2002; Motamedi and Meador 2003). AEDs are of special interest as they form the principal treatment option for GGE (Loring and Meador 2004). Depending on AED type, several fields of cognition are affected including memory and attentional capabilities under Phenorbital- or Topiramate-treatment respectively (Ijff and Aldenkamp 2013). However, irrespective of AED-type, polytherapy was found to increase cognitive dysfunction in patients with epilepsy (Ijff and Aldenkamp 2013).

Concerning the interaction between connectivity and cognitive performance in GGE, a positive correlation between FC and performance in an attention task was found (Killory et al. 2011). However, this was only tested on CAE patients. For patients with JME, an increased FC was observed by fMRI together with greater demand in a working memory task (Vollmar et al. 2011). Nevertheless, to the author's knowledge, research about correlation between FC and cognitive performance in GGE is in general scarce.

With the effects of medication and FC in mind, it is difficult to explain whether cognitive changes are caused by stable factors of the disease, such as an altered connectivity, or by external factors like AEDs (Motamedi and Meador 2003; Aldenkamp and Arends 2004). Therefore, another goal of this thesis is to explore the interactions between cognitive performance and AEDs respectively FC/power.

1.5 Objectives of this Study

As discussed in section 1.2, GGE patients showed an increased FC and power compared to healthy controls in several frequency bands. This has, however, only been addressed by a few studies using source-based connectivity analyses. Furthermore, out of these studies only MEG was used to determine connectivity measures. To add another methodological perspective and to compare results, EEG-recordings from the same patients studied by Stier et al. (2021) in MEG were used to calculate FC and power. Thus, the question arises as to whether similar findings can be observed as were reported for MEG.

The **first hypothesis** is therefore that, not only do GGE patients show an increased power and FC compared to healthy controls, in addition they also show increases in source-reconstructed vertex and global EEG.

The **second hypothesis** focuses on the substantiation of the effects of clinical variables for which significant differences were observed by Stier et al. (2021) using MEG. Patients who showed GSWDs in initial recordings should have an increased FC/power compared to those who were GSWD-free (**2a**). Having had seizures in the recent past should not result in significant FC changes (**2b**). Lastly, as the number of AEDs taken showed a negative correlation with FC and power in MEG, similar results are expected in the EEG-analysis (**2c**).

The **third hypothesis** is that, due to the interference of AEDs with cognitive performance as described in section 1.4, patients who take more AEDs perform worse on cognitive tests than those who take fewer. In addition, as the relationship between cognitive performance

and connectivity is not well understood, the thesis will also explore whether increased FC/power can be observed along with better cognitive performance or the other way round.

2 Method

2.1 Study Design

Data acquisition took place at the university hospital in Tübingen between 2018 and 2019. The study was approved by the local Ethics Committee of the medical faculty of the University of Tübingen (reference number: 646/2011BO1) and was in accordance with the Declaration of Helsinki (World Medical Association 2008).

The examination of each participant usually began with MEG- and EEG-acquisitions, both lasting 30 minutes. One hour of neuropsychological testing was carried out subsequently and finally, participants underwent 30 minutes of MRI-scan. However, for this thesis only the EEG-analysis, anatomical MRI-scans and neuropsychological testing were part of investigation.

2.2 Participants

For this study, data of a total of n = 25 patients diagnosed with GGE according to the ILAE classification (Scheffer et al. 2017), and n = 40 healthy controls were included. Recruitment of patients was done through the Department of Neurology of the University Hospital of Tübingen. Controls were found via advertisement at the university, the university hospital and throughout the area of Tübingen. In 22 out of 25 patients GSWDs had been observed via EEG in past medical history. Furthermore, the epilepsy-subsyndromes were found as follows in the patient sample: five patients were diagnosed with CAE, six with JAE, five with JME, four with iGTCS and for five patients no further classification was possible. In nine out of 25 patients, the EEG-analysis revealed GSWDs, whereas none were found in the controls. Three out of 25 patients revealed abnormalities in anatomical MRI scans with two showing uncomplicated cysts and one presenting with a single white matter lesion. Anatomical scans of controls were visually rated as normal. While all controls had a negative family history in terms of epilepsy or seizures, 12 patients reported having at least another family member with an epileptiform disease. All controls were healthy, showed no psychiatric or neurological disease, had never experienced seizures and were free of medication at the time of data acquisition. All but two patients took AEDs at the time of the study (M = 1.2 drugs, SD = 0.65). Both groups were matched for age ($M_{patients}$ = 31.71 = 12.16; $M_{controls}$ = 30.07, SD = 11.11, W = 472, p = 0.71) and sex (female: 56 % patients, 50 % controls; X^2 (1, N = 65) = 0.05, p = 0.83)

2.3 EEG Signal Processing

The preparation of the EEG-signal was performed using the fieldtrip toolbox in MATLAB (version 9.0, R2016a, Mathworks Inc.; Oostenveld et al. 2011). As a first step, EEG data was pre-processed. This included downsampling of the signals from originally 1 kHz - 150 Hz, line-noise-removal and filtering the signal to 1 - 70 Hz. Next, the course of each individual dataset was visually reviewed to get a first impression of the data quality. The signal was inspected in data segments of 10 s length over all 256 channels. This enabled identification and thus exclusion of data with sensor jumps, movement artefacts, or excessive muscle activity from the analysis-data. Afterwards, an independent component analysis (ICA) was performed to identify eye-movement activity and the electrocardiographic signal. Another visual inspection of the dataset followed evaluating subjects' vigilance. This was rated in accordance with the sleep scoring criteria of the American Academy of Sleep Medicine (Berry et al. 2015). Furthermore, extant artefacts which were not caught by the first visual inspection or ICA were ruled out. Then, the presence of GSWDs was evaluated. Segments showing GSWDs were rejected from further analysis, including one segment immediately before and after the GSWD. This resulted in a total of 30 s of signal being eliminated for each GSWD-segment found. Eventually, each dataset was cleared down to at least 5 min (= 30 trials) of clean data, being free from GSWDs, sleep and artefacts. From these cleaned trials 30 were randomly selected to be used for the following source analysis. In accordance with Stier et al. (2021), six conventional frequency bands were chosen (delta: 2 ± 2 Hz, theta: 6 ± 2 Hz, alpha: 10 ± 2 Hz, beta1: 16 ± 4 Hz, beta2: 25 ± 4 Hz and gamma: 40 ± 8 Hz).

In order to project the EEG-data into the source space, a beaming algorithm was used (Gross et al. 2001). Lead field matrices were determined for each vertex point of subjects' individual cortical meshes. For each frequency band mentioned in the previous section, an adaptive spatial filter was administered (regularization: lambda = 5 %).

Coherency as a measure of phase synchrony between two signals was calculated between all pairs of sources (n = 2338). The referring coefficient used in this analysis is called imaginary part of coherency (CohImg). It filters out any perfect coherency values as these are likely to occur due to similar sources being measured by the respective electrodes (Nolte et al. 2004). This procedure led to the construction of an undirected, symmetrical, and weighted matrix of FC for each frequency band and participant. In these, CohImg would define weights and vertices the nodes. To determine general connection strength of a vertex, weights of each vertex were averaged. Furthermore, power was determined for every source position as squared amplitude. Lastly, global power and global connectivity were calculated to create

overall indicators of the metrics. Therefore, power and CohImg respectively were averaged across all vertices. This resulted in one global value per frequency per subject for each of the two statistical metrics.

2.4 Individual Head Modelling

For the construction of subjects' individual head models, sagittal high-resolution T1-weighted images were obtained for all participants (3D-MPRAGE, repetition time = 2.3 s, echo time = 3.03 ms, flip-angle = 8°, voxel size = 1 x 1 x 1 mm). This was either done on a Siemens Magnetom Trio 3T scanner (Siemens AG, Erlangen, Germany) equipped with a 12-channel head coil (11/40 controls, 5/25 patients) or with the Siemens Magnetom Primsa 3T system (Siemens, AG, Erlangen, Germany) with a 64-channel head coil (29/40 controls, 20/25 patients). To reconstruct cortical surfaces the FreeSurfer software package was used (Fischl 2012). Afterwards, reduction of the cerebral cortical surface to 1002 common vertices per hemisphere was done using SUMA (Saad and Reynolds 2012). The original surface of each subject was then resampled with the 'fsaverage' template (density factor ld = 10). Besides smoothing the junction between white and grey matter ("smoothwm surface"), six subcortical nuclei, namely bilateral hippocampus, thalamus, caudate, putamen, pallidum, and amygdala, were reconstructed using the "fsaverage" template atlas. For surface conversion of each region, Matlab (isosurface) was used. Each region was then resampled to a number of vertices which is consistent with their average volume compared to the SUMA reconstruction respectively (334 vertices; 167 per hemisphere). In order to achieve spatial normalization, subcortical reference surfaces were transferred to MNI space using DARTEL normalization (Ashburner 2007) in SPM12 (Penny et al. 2011). Its brain model is based on the segmented "fsaverage" brain and uses the CAT12 DARTEL template as a target (Gaser and Dahnke 2016). Next, subjects' MRI images were segmented using SPM12 (unified segmentation) and afterwards adapted with DARTEL and its CAT12 template (Ashburner and Friston 2005). The described process eventually led to a total of 2338 vertex positions for each participant. A point-for-point anatomical correspondence for both cortical and subcortical regions was achieved (via SPM/DARTEL and FreeSurfer/SUMA respectively). EEG electrodes were reordered according to anatomical landmarks. They were then estimated onto the scalp mesh which was created during segmentation. A three-layer boundary model was used to calculate leadfields (dipoli; standard-values of scalp = 0.33, skull = 0.0041 and brain = 0.33)

2.5 Statistical Analysis Procedure

A nonparametric statistical tool for surface-based-data was used for the statistical metrics of the EEG-analysis, namely Permutation Analysis of Linear Models (PALM; Winkler et al. 2014). For group comparisons, t-contrasts were performed, and the group's contrasts were created separately for every frequency band on a global level based on vertices. To carry out comparisons, a general linear model was fitted for every permutation, which included the named imaging metrics as dependent variables and group association, sex, and age as predictors. A tail approximation with 500 permutations was used for calculations of power and CohImg contrasts. P-values were estimated based on the underlying empirical distribution of t-statistics. Threshold-free cluster enhancement (TFCE; Smith and Nichols 2009) was performed and familywise-error-correction (FWE) of p-values to account for multiple comparisons was used. This statistically enforced those clusters which consisted of nearby significant vertices, instead of single ones that reached significance. Values are indicated as -log10 P, significance threshold was 1.3 (= $p < 0.05$).

To analyse effect sizes for both global and vertex-based group comparisons, Cohen's d were obtained from the t-statistics of the linear models yielding in an age and sex adjusted d. Effect sizes can be interpreted as follows: $d = 0.2$ is a small effect, $d = 0.5$ intermediate and $d = 0.8$ large (Cohen 1992).

2.6 Neuropsychological Assessment

Nineteen out of 25 GGE patients underwent additional neuropsychological testing. Relevant tests included the "d2-R. Aufmerksamkeits- und Konzentrationstest", a test for measuring attention, concentration span and working speed (Brickenkamp et al. 2010). Participants were asked to read through rows of letters, with each letter surrounded by several lines. The task was to cross out only the letter "d", and only when it was accompanied by two lines, as fast as possible without making mistakes.

Next, the so called "Verbaler Lern- und Merkfähigkeitstest" (VLMT), a German version of the American auditory verbal learning test for measuring verbal memory, was carried out (Helmstaedter and Durwen 1990; Schmidth 1996). For this test subjects underwent five trials. For each trial they attempted to learn a list of the same 15 semantically independent words. After each trial they were asked to recall the words. A single trial consisting of 15 new words followed for interference. Subjects were then asked to immediately recall the original word list and again one half-hour after being distracted.

Afterwards, the "Diagnosticum für Cerebralschädigung-II" (DCS-II) was performed. It is a tool that is sensitive to figural learning and memory deficits, in which subjects must memorize and reproduce a series of nine figures by using five equally long wooden sticks. A total of six learning trials is offered to complete the task (Weidlich et al. 2011).

The Trail Making Test (TMT) captures various cognitive functions such as working memory and attention. The task is to connect 25 circles containing either letters or numbers as fast as possible. Two versions, TMT A and TMT B were performed, with the latter being more complex as participants must switch between alphabet and sequence of numbers. For both versions time is recorded (Reitan 1992).

Another test used for the study is the Porteus Maze test, a procedure that is sensitive to psychomotor coordination. Participants must draw a pencil line out of a printed picture of a labyrinth as quickly as they can. For each subject, two versions of the labyrinth are presented, one with low and one with high difficulty (Porteus 1956).

The digit-span test was used to measure working memory, verbal recall, and attentional capacity. For this test participants were required to memorize an increasing row of single digits which they then were immediately asked to reproduce in the same or in reversed order (Töne-Otto 2009).

Also, the Tower of London task was carried out. It is a test to measure problem solving skills in which three balls, different in size, are distributed among rods of various lengths. The subjects task is to sort the balls according to their size on one rod while using as few turns as possible (Shallice 1982).

The "Mehrfachwahl-Wortschatz Test" (MWT) was used as a premorbid measurement for general intelligence. Subjects were presented with a list of words with each line containing one real and four fake words. The task is to identify the actual words from each line (Lehrl 2005).

At the end, the beck depression inventory 2 (BDI-2) was performed. It is a questionnaire scanning for depressive symptoms, in which subjects are asked to rate a number of statements concerning 21 items, for example "Traurigkeit" (Beck et al. 2009). When testing cognitive performance, it is important to scan for depressive symptoms as depression or other mood disorders can interfere with cognitive abilities or speed (Zhou et al. 2021).

3 Results

3.1 Functional Changes in GGE

3.1.1 Vertex-based and Global Analyses of EEG Data

In comparison to healthy controls, patients showed an increased FC in delta, theta and alpha using vertex-based analysis. The strongest effects were found in theta with an emphasis on parietal and temporal regions (s. Figure 4). No effects were found for subcortical regions, which is why visualizations focus on cortical regions.

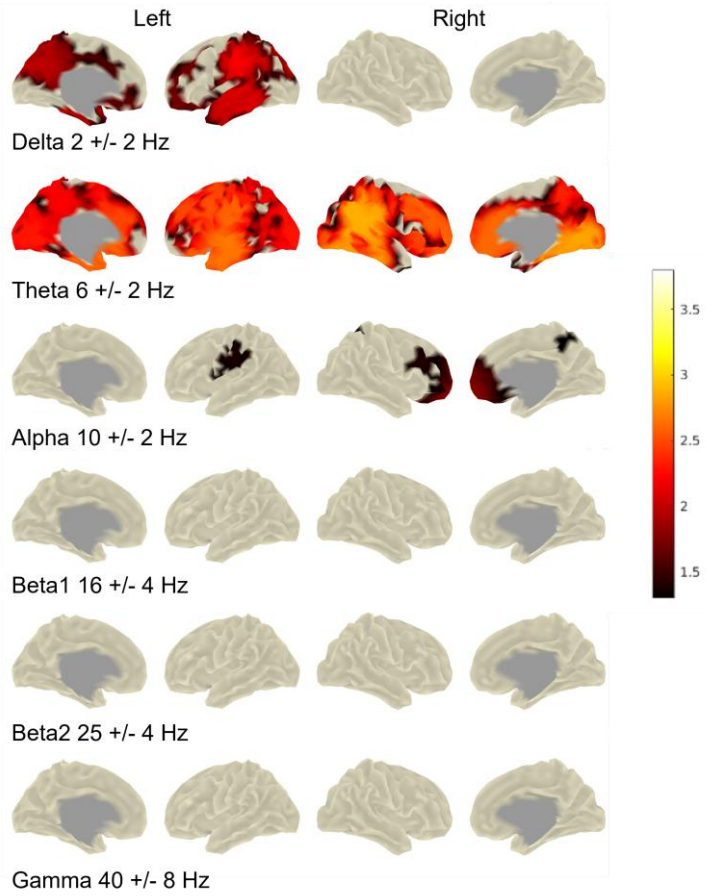

Figure 4: Vertex-based connectivity-comparison of patients and controls. This was performed for each frequency band using imaginary part of coherency as connectivity measure**.** The plot displays significant vertices (-log10 p-threshold of 1.3, equivalent to $p < 0.05$), that is significantly increased connectivity, in patients with GGE compared with controls. Results are family-wise-error corrected. Subcortical data are not shown as none reached significance.

On a global level, the same contrast also revealed significant increases in FC for patients in delta ($t = 2.52$, $p = 0.008$, $d = 0.65$), theta ($t = 3.63$, $p < 0.001$, $d = 0.93$) and alpha ($t = 2.05$,

p = 0.02, d = 0.53) but not within the other frequencies (beta1: t = 1.21, p = 0.12, d = 0.31; beta2: t = 0.69, p = 0.25, d = 0.18; gamma: t = 0.15, p = 0.45, d = 0.04, s. Figure 5).

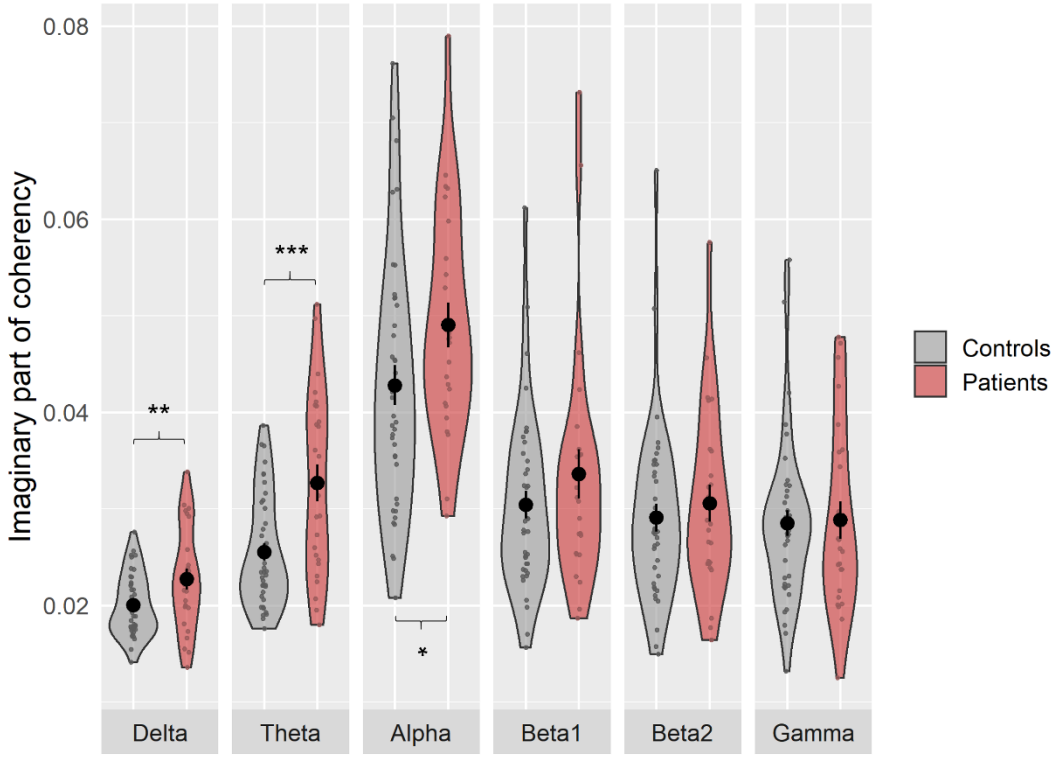

Figure 5: Global based connectivity-comparison of patients and controls. Violin-plots are shown for each frequency band using imaginary part of coherency. Central dots indicate group-mean, black lines represent standard error, grey dots individual data points in arbitrary units (* p < 0.05, ** p< 0.01, *** p < 0.001).

In terms of power, patients showed increased power compared to controls on a vertex-level across all frequencies with the strongest effects in parietal and frontal areas (s. Figure 6).

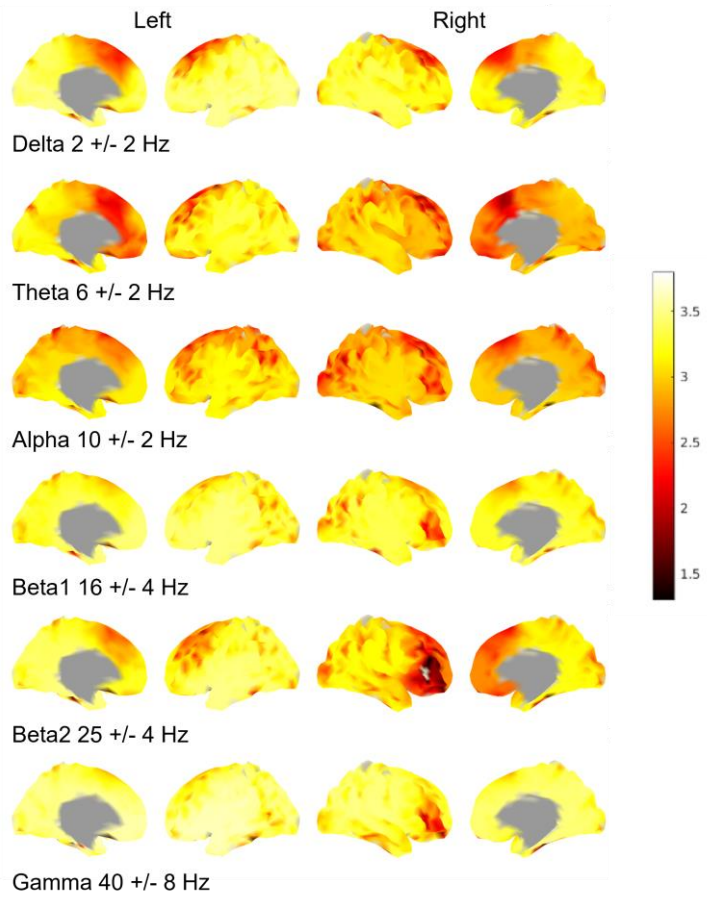

Figure 6: Vertex-based power-comparison of patients and controls. This was done for each frequency band. The plot displays significant vertices (-log10 p-threshold of 1.3, equivalent to $p < 0.05$), that is significantly increased power, in patients with GGE compared with controls. Results are family-wise-error corrected. Subcortical data are not shown as none reached significance.

Similar effects could be observed in the global analysis (delta: $t = 4.22$, $p < 0.001$, $d = 1.08$; theta: $t = 3.41$, $p < 0.001$, $d = 0.88$; alpha: $t = 3.9$, $p < 0.001$, $d = 0.1$; beta1: $t = 4.49$, $p < 0.001$, $d = 1.15$; beta2: $t = 4.44$, $p < 0.001$, $d = 1.14$; gamma: $t = 4.9$, $p < 0.001$, $d = 1.25$; s. Figure 7).

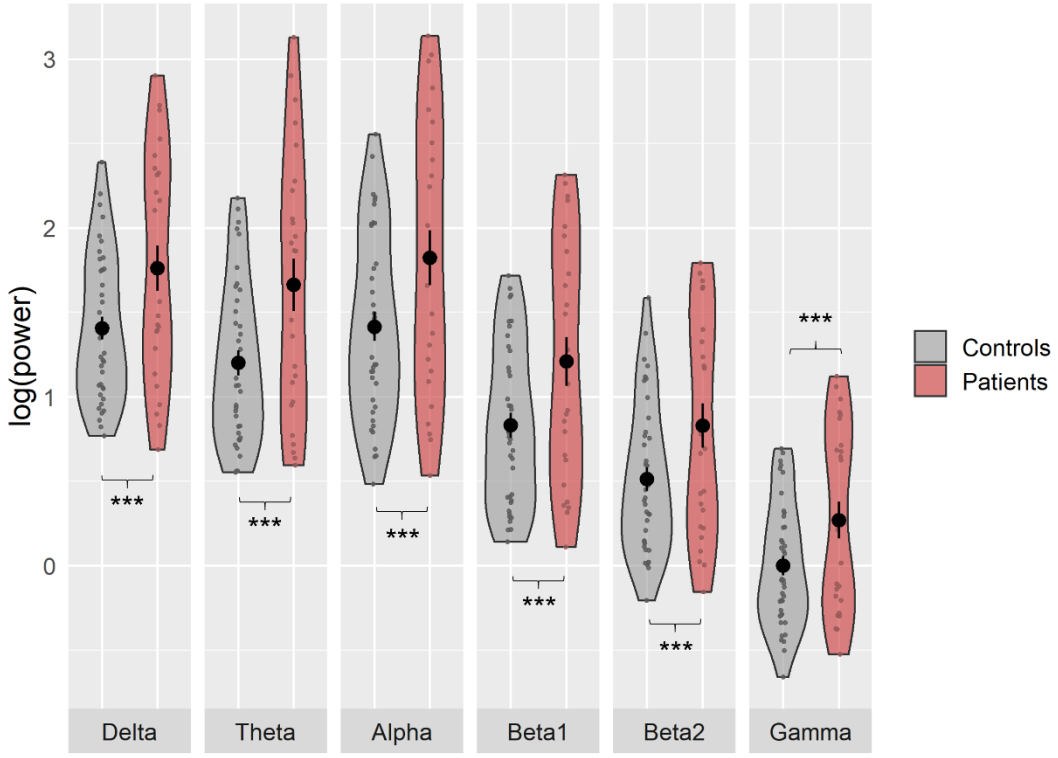

Figure 7: Global based power-comparison of patients and controls. Violin plots are shown for each frequency band using the 10-logarithm of power. Central dots indicate group-mean, black lines represent standard error; grey dots represent individual data points in arbitrary units (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

3.1.2 EEG-Analyses of Clinical Variables

The influence of three clinical variables on the EEG signal was investigated: the presence of GSWDs in the recordings, the occurrence of seizures within the last 12 months prior to investigation and the number of AEDs used on the day of investigation. For each of the mentioned variables, the patient cohort was divided into two. The first was split into those who showed no GSWDs in the EEG recordings (n = 16) and those who did (n = 9). For the second variable, one group included those who reported having no seizures within the 12 months prior to investigation (n = 16) and the other those who had at least one (n = 9). For the use of AEDs, patients were divided whether they took at least two AEDs (n = 18) or less (n = 7) at the time of investigation. To study the effects of the aforementioned clinical variables, two-sample comparisons between patient-subgroups were performed for each of the three.

When comparing patients who showed GSWDs in the EEG-data to those who did not, significant differences in EEG emerged only in CohImg, not in power. Vertex-based analysis

revealed higher connectivity in delta and gamma for those with GSWD. The strongest effects were observed in the left supramarginal area in the delta frequency band (s. Figure 8).

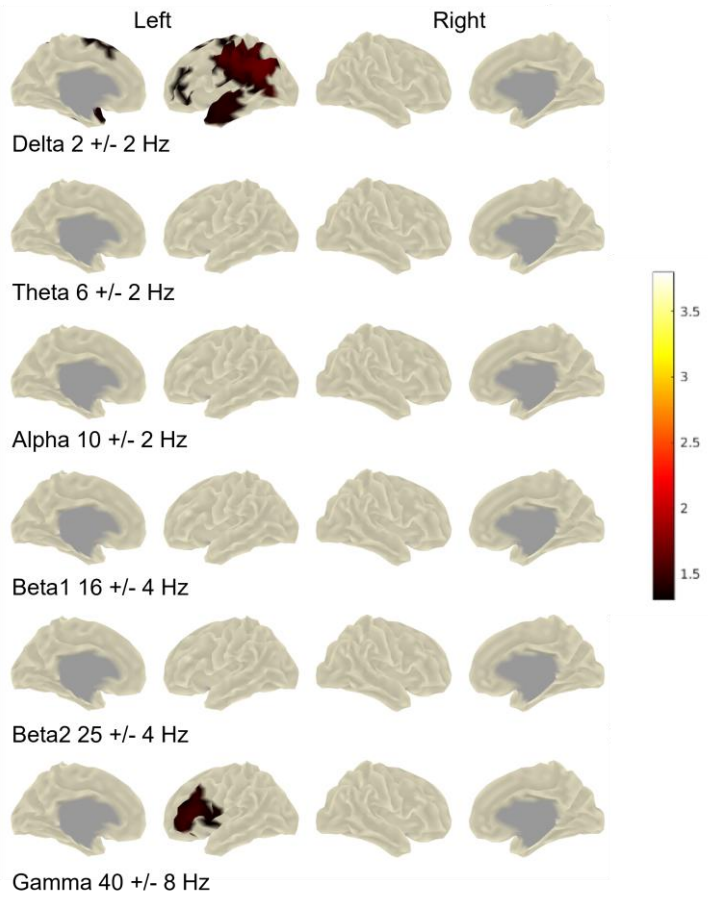

Figure 8: Vertex-based connectivity-comparison of patients with and without generalized-spike-wave-discharges (GSWD) in the recordings. Data are shown for each frequency band using imaginary part of coherency. The plot displays significant vertices (-log10 p-threshold of 1.3, equivalent to $p < 0.05$), that is higher connectivity, for patients with GSWDs. Results are family-wise-error corrected. Subcortical data are not shown as none reached significance.

The analysis on a global level also showed larger connectivity for patients with GSWDs, however, significance was only reached in gamma ($t = 1.92$, $p = 0.04$, $d = 0.81$) not in the other frequency bands (delta: $t = 1.7$, $p = 0.05$, $d = 0.72$; theta: $t = 1.58$, $p = 0.07$, $d = 0.67$; alpha: $t = 0.35$, $p = 0.35$, $d = 0.15$; beta1: $t = 1$, $p = 0.17$, $d = 0.42$; beta2: $t = 1.37$, $p = 0.09$, $d = 0.58$; s. Figure 9).

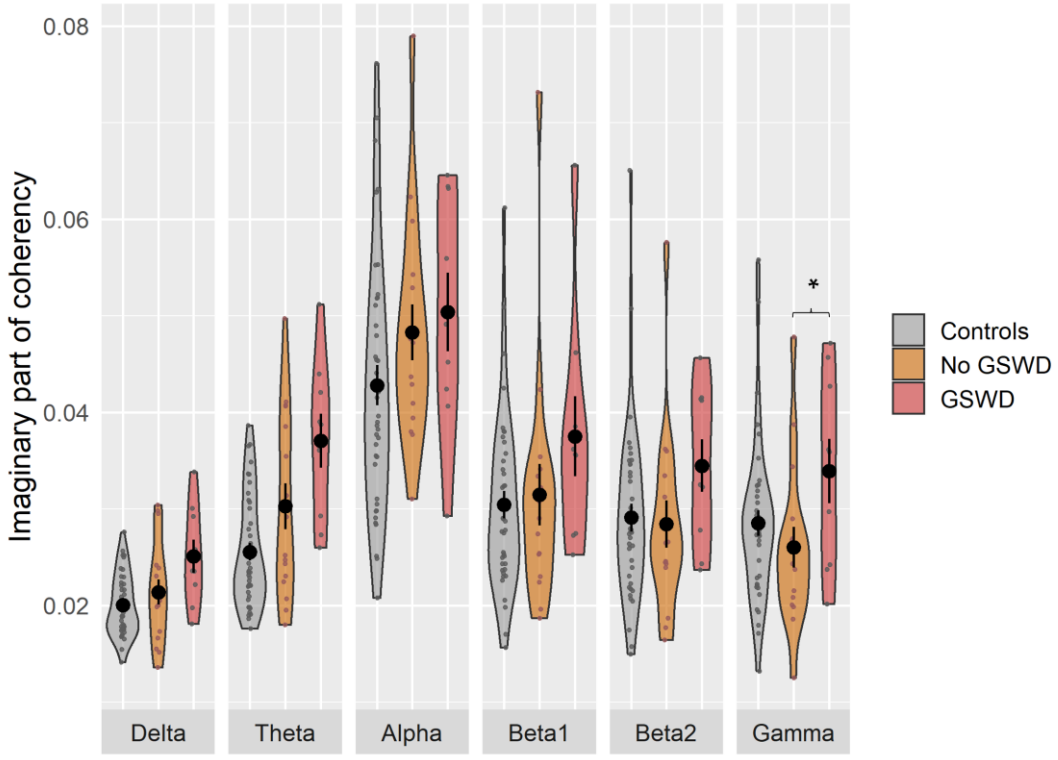

Figure 9: Global connectivity-comparison of controls, patients with and without general-spike-wave-discharges (GSWD) in the recordings. Data are shown for each frequency band using imaginary part of coherency. Central dots indicate group-mean, black lines represent standard error, grey dots individual data points in arbitrary units (* $p < 0.05$).

Patients who reported having had seizures within 12 months prior to the investigation presented with a lower power than those who were seizure-free in that period. On vertex-based calculations this pattern was found to be significant in alpha, beta1, beta2 and gamma, with the latter two showing the strongest effects, especially in frontal and parietal regions bilaterally. CohImg analysis, however, revealed no significant differences (s. Figure 10).

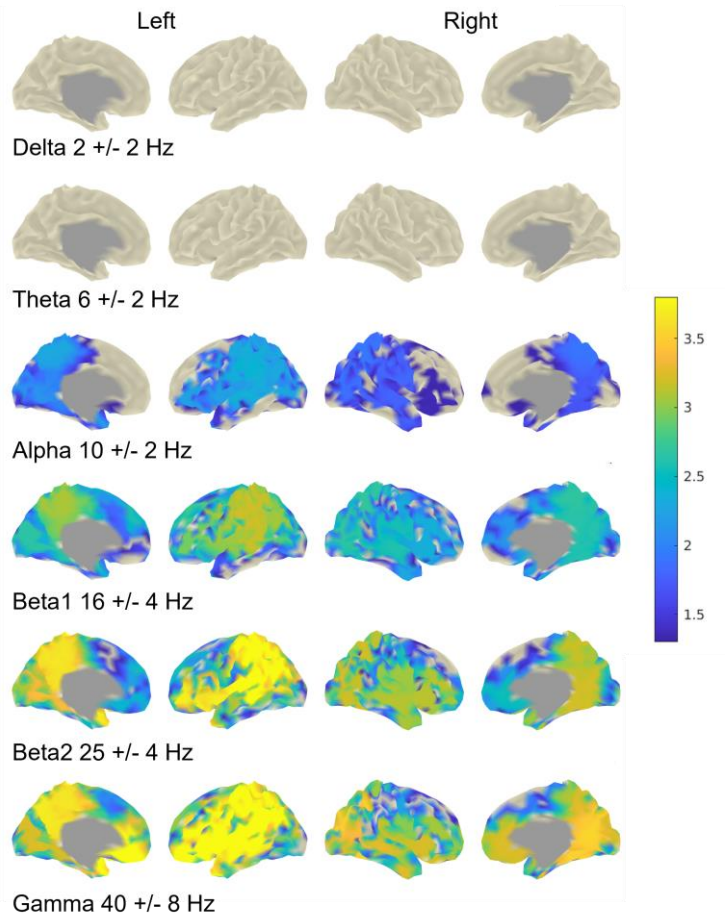

Figure 10: Vertex-based power-comparison of patients with and without seizures. Data are shown for each frequency band. Patients were divided into those who reported having seizures in the last 12 months prior to the investigation and those who were seizure-free for that period. The plot displays significant vertices (-log10 p-threshold of 1.3, equivalent to $p < 0.05$), that is larger power for patients who were seizure-free in the mentioned time period. Results are family-wise-error corrected. Subcortical data are not shown as none reached significance.

Analysis of global mean values resulted in similar observations. While connectivity remained non-significant, power analysis showed significantly lower power in alpha ($t = 2.18$, $p = 0.02$, $d = 1.02$), beta1 ($t = 2.75$, $p = 0.004$, $d = 1.28$), beta2 ($t = 3.45$, $p < 0.001$, $d = 1.6$) and gamma ($t = 3.45$, $p < 0.001$, $d= 1.6$) for patients with seizures when compared to those without but not in delta ($t = 0.76$, $p = 0.24$, $d = 0.35$) or theta ($t = 0.25$, $p = 0.43$, $d = 0.12$). For this variable, a strong sex bias (Group 0: 69% females, group 1: 33% females) could, however, limit interpretation of observed results.

A significantly lower connectivity was found for patients who took at least two AEDs than for those who took only one or none. This was observed on a vertex-based level in delta, with an emphasis on the superior right temporal cortex (s. Figure 11).

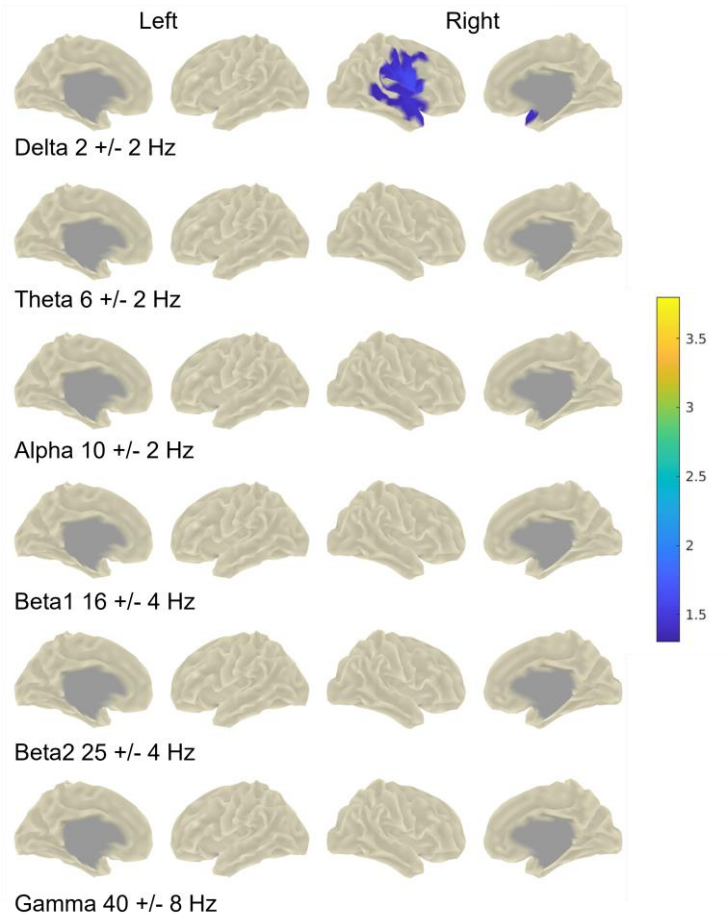

Figure 11: Vertex-based comparison of patients with low and high drug load. Results are shown for each frequency band using imaginary part of coherency. Division of patients was performed according to those who took two or more anti-epileptic drugs (AED; high drug load) at the time of investigation and those who took one or no AED (low drug load) for each frequency band. The plot displays significant vertices (-log10 p-threshold of 1.3, equivalent to $p < 0.05$), that is larger connectivity for patients who took one or no AED. Results are family-wise-error corrected. Subcortical data are not shown as none reached significance.

When considering the comparison of global values, as calculated by CohImg, delta also showed a significant decrease in FC for patients with more than one AED ($t = 1.2$, $p = 0.03$, $d = 0.9$). The other frequency bands showed a similar descriptive pattern but did not reach significance (theta: $t = 0.99$, $p = 0.17$, $d = 0.45$; alpha: $t = 0.88$, $p = 0.19$, $d = 0.4$; beta1: $t = 1.53$, $p = 0.06$, $d = 0.69$; beta2: $t = 0.62$, $p = 0.28$, $d = 0.28$; gamma: $t = 0.86$, $p = 0.21$, $d = 0.39$; s. Figure 12). Power analysis revealed no significant differences, neither on vertex-based nor global level, however, there was a similar trend as observed for CohImg (delta: $t = 1.04$, $p = 0.14$, $d = 0.47$; theta: $t = 1.09$, $p = 0.13$, $d = 0.49$; alpha $t = 1.00$, $p = 0.17$, $d = 0.45$; beta1: $t = 0.81$, $p = 0.22$, $d = 0.36$; beta2: $t = 0.09$, $p = 0.47$, $d = 0.04$; gamma: $t = 0.52$, $p = 0.32$, $d = 0.23$).

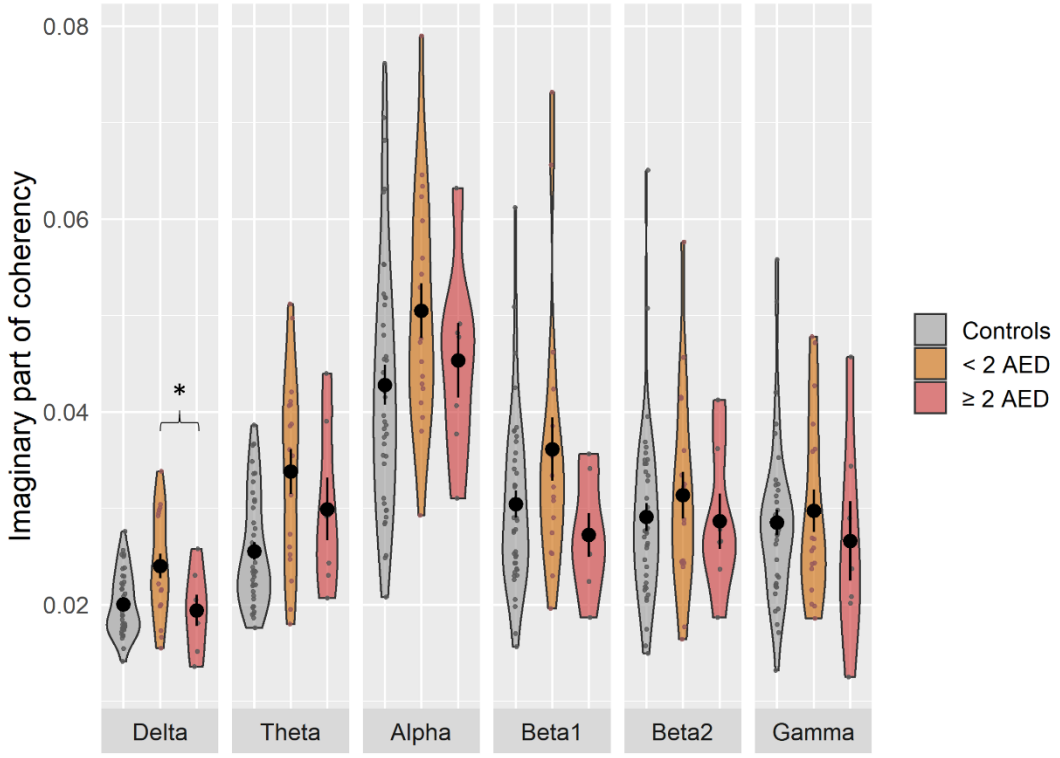

Figure 12: Global connectivity-comparison of controls, patients with low and high drug load. Results are shown for each frequency band using imaginary part of coherency. Division of patients was performed according to those who took two or more anti-epileptic drugs (AED; high drug load) at the time of investigation and those who took one or no AED (low drug load) for each frequency band. Central dots indicate group mean, black lines represent standard error (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$), grey dots represent individual data points in arbitrary units.

3.2 Neuropsychology in GGE

It was important to first determine whether the performance of the patient sample would deviate from a hypothetical population mean. This was analysed by non-parametric one-sample-wilcoxon-tests. As can be seen in Table 1, the patient sample differed significantly in several tests, including memory, intelligence, problem solving and mood. However, only the test for the total number of recalled elements in the DCS2 survived the correction for multiple comparisons ($Z = 190$, $p < 0.001$).

Table 1: Significant differences in cognitive performance within the patient sample.

Test-Variable	p-level	Test-Variable	p-level
Memory		**Attention**	
VLMT_Dg7	**	D2_F%	*
VLMT_P	*	**Intelligence**	
VLMT_In	**	MWT	**
VLMT_FP	**	**Problem-solving**	
DCS2_Rcum	***	TOL	*
DCS2_LEI	**	**Mood**	
		BDI	**

One-sample-wilcoxon-ranked-tests were performed within the patient sample relative to reported test metrics. Double underlining of asterisks indicates analysis survived Bonferroni-correction (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). D2 = D2-attentional test; VLMT = Verbal Learning Memory test; DCS2 = Diagnosticum für Cerebralschädigung; MWT: Mehrfachwahl Wortschatz Test; TOL = Tower of London; BDI = Beck-Depressions-Inventory. The letters following the test name represent sub-scores of the respective test. D2_F%: Percentage of mistakes made in the D2, VLMT_Dg7: Number of recalled words in the last run-through of the test, VLMT_P: Number of perseverance errors, VLMT_In: number of inversion errors, VLMT_FP: number of false positive errors, DCS2_Rcum: total sum of recalled figures, DCS2_LEI: learning index

3.2.1 Current Medication

To analyse the association between medication and cognitive performance, initial non-parametric Mann-Whitney tests were performed between the two patient samples mentioned in section 3.1.2. Detailed results can be seen in Table 2. Patients who took less medication ($n = 7$) performed better for the first trial in the TMT than those with more medication ($n = 18$; $U = 15$, $p = 0.04$). This pattern was inverted in the VLMT, as patients who took more AEDs performed better in the first recall of words ($U = 16.5$, $p = 0.046$) as well as in the number of perseveration mistakes ($U = 65$, $p = 0.02$). All in all, none of these comparisons survived Bonferroni-correction.

Table 2: Differences in cognitive performance between patients with low and high drug load.

Test-variable	< 2 AEDs	≥ 2 AEDs	p-level
Psychomotor speed			
TMT_A	-0.18 (1.39)	-1.08 (0.87)	*
Memory			
VLMT_Dg1	0.09 (0.89)	1.22 (0.82)	*
VLMT_P	0.09 (0.36)	0.52 (0.24)	*

Comparison of patients who took less than two ("< 2 AEDs"; low drug load, n = 13) and patients who took at least 2 anti-epileptic-drugs (AED; "≥ 2 AEDs"; high drug load, n = 6) at the time of investigation. Means of z-standardised values with standard deviation in parentheses. Higher values indicate better performance (* $p < 0.05$); TMT = Trail Making Test; VLMT = Verbal Learning Memory Test. Letters following the test name represent sub-scores of the respective test. TMT_A: Score of the first trial, VLMT_Dg1: number of recalled words in the first trial, VLMT_P: number of perseverance errors.

To account for the potential influence of other variables, further regression models with cognitive test performance as dependent variable, and medication, age, sex, and global FC/power at each frequency band were created. Results showed a better performance in attention for those who took fewer AEDs. However, this pattern was different for the first recall of VLMT and the number of perseverance mistakes in VLMT as patients with two or more performed better than those with fewer AEDs. Results persisted when global FC/power as predictor was excluded. Detailed results can be found in Table 3. Note that none of the results survived Bonferroni-correction.

Table 3: **Regression-coefficients of the medication variable in association with cognition.**

A

CohImg	**w.E.**	**Delta**	**Theta**	**Alpha**	**Beta1**	**Beta2**	**Gamma**
Attention							
D2_GZ	-0.93	**-1.34***	**-1.10***	-0.97	-0.85	-0.88	-0.84
D2_GZF	-0.74	**-1.17***	-0.88	-0.76	-0.63	-0.66	-0.62
D2_KL	-1.04	**-1.60***	-1.15	-1.01	-1.02	-0.98	-0.94
Memory							
VLMT_Dg1	**1.12***	1.18	**1.10***	**1.17***	**1.34***	**1.23****	**1.28****
VLMT_P	**0.41***	0.38	**0.40***	**0.40***	**0.46***	**0.39***	**0.37***

B

Power	**w.E.**	**Delta**	**Theta**	**Alpha**	**Beta1**	**Beta2**	**Gamma**
Attention							
D2_GZ	-0.93	**-1.06***	**-1.12***	-0.98*	**-1.03***	-0.93	-0.95
D2_GZF	-0.74	-0.88	**-0.93***	-0.79	-0.85	-0.74	-0.75
D2_KL	-1.04	**-1.26***	**-1.24***	-1.09	-1.19	-1.03	-1.06
Memory							
VLMT_Dg1	**1.12***	**1.15***	**1.10***	**1.13***	**1.17***	**1.12***	**1.15***
VLMT_P	**0.41***	**0.38***	**0.38***	**0.40***	**0.40***	**0.41***	**0.40***

The regression was fit as follows: Neuropsychological test score (z-standardised) = age + sex + global-EEG-score (for each frequency band; **A**: imaginary part of coherency (CohImg); **B**: power) + medication (0 = < 2 anti-epileptic-drugs (AED), 1 = ≥ 2 AEDs). Positive values indicate better performance under more AEDs (* $p < 0.05$, ** $p < 0.01$); w.E. = without global-EEG-score as predictor; D2 = D2-attentional test, VLMT = Verbal Learning Memory Test. Letters following the test name represent sub-scores of respective tests. D2_GZ = number of processed digits, D2_GZF: number of correctly processed digits, D2_KL: concentration performance, VLMT_Dg1 = number of recalled words in the first trial, VLMT_P = number of perseverance errors.

3.2.2 Connectivity and Power

The relationship among EEG FC, power and cognitive performance showed a different pattern. When looking at the regression coefficients of respective global means in the same models as seen in section 3.2.1, higher FC/power was associated with worse cognitive performance in the lower frequency bands (delta, theta, and alpha) in areas such as attention, memory and problem-solving. For higher frequencies however, higher FC/power indicated a better performance in cognition (e. g. working memory, attention, and memory). After Bonferroni-correction only two effects persisted. (s. Table 4).

Table 4: Regression-coefficients of global connectivity/power in association with cognition.

A

CohImg	Delta	Theta	Alpha	Beta1	Beta2	Gamma
Working memory						
Zah_R	33.84	4.53	28.5	45.8	**92.46****	**96.03****
Zah_Ges	43.37	1.48	-5.98	31.95	**75.17***	**71.65***
Attention						
D2_GZ	-97.72	**-52.92***	-11.45	9.94	31.71	30.65
D2_KL	**-134.53***	-35.17	8.71	1.6	34.36	31.5
D2_F%	**-188.6****	-49.46	16.51	-0.92	41.09	52.54
Memory						
VLMT_Dg1	-12.75	-6.97	17.0	25.42	**63.4***	46.79
VLMT_Dg5	55.4	33.03	29.12	30.62	**69.71****	**60.53***
VLMT_Dg15	82.73	27.01	24.22	36.0	**89.1****	**79.95****
VLMT_I	100.53	26.56	22.03	**67.85****	**110.25*****	63.11
VLMT_W	-43.22	**-40.0***	-8.46	14.72	18.11	30.85
Problem-Solving						
TOL	-96.52	**-72.57***	-21.41	-23.07	38.67	80.34

B

Power	Delta	Theta	Alpha	Beta1	Beta2	Gamma
Working memory						
Zah_V	0.91	0.4	0.45	1.35	**2.09***	2.46
Attention						
D2_GZ	-1.37	**-1.72****	-1.35*	-1.32	-0.8	-0.83
D2_GZF	-1.42	**-1.68***	-1.34	-1.35	-0.76	-0.68
D2_KL	**-2.3***	**-1.87***	**-1.76***	-1.99	-1.36	-1.38
Psychomotor speed						
TMT_A	-1.81	-0.48	-0.79	-2.1	**-3.01***	-2.96
Memory						
VLMT_WF	-1.4	**-1.22****	-0.89	-1.14	-0.95	-0.61

The regression model looked as follows: Neuropsychological test score (z-standardised) = age + sex + global-EEG-score (for each frequency band; **A**: imaginary part of coherence (CohImg); **B**: power) + medication (0 = < 2 anti-epileptic-drugs [AED], 1 = ≥ 2 AEDs); Positive values indicate better performance with growing connectivity/power (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). Double underlining of asterisks indicates analysis survived Bonferroni correction; Zah = digitspan test, D2 = D2-attentional test, TMT = trail making test, VLMT = Verbal Learning Memory Test, TOL = Tower of London, BDI = Beck depression inventory. Letters following the test name represent sub-scores of the respective test. Zah_V: recalled digits in forward-trial, Zah_R: recalled digits in backward trial, Zah_Ges: total number of recalled digits, D2_GZ: number of processed digits, D2_GZF: number of correctly processed digits, D2_KL: concentration performance, D2_F%: Percentage of mistakes, TMT_A: Score of the first trial, VLMT_Dg1: number of recalled words in the first trial, VLMT_Dg5: number of recalled words in the fifth trial, VLMT_Dg15: total number of recalled words in the first five trials, VLMT_Dg7: number of recalled words in the last trial, VLMT_I: number of recalled words for the inversion list, VLMT_W: number of recognized words, VLMT_WF: number of recognized words after error subtraction.

4 Discussion

This thesis explored the differences in FC and power of EEG signals between GGE patients and healthy controls. Increased FC and power were observed for patients. The influence of clinical variables on functional metrics was also observed. On the one hand, having had GSWDs in the recorded EEG was associated with a higher FC than without. On the other hand, a growing number of used AEDs was associated with a reduced FC. Also, patients who had seizures in the recent past showed a reduced power. As the last focus, associations between cognitive performance and AEDs, or FC/power respectively, were investigated. While attention was worse in the group with higher number of AEDs, performance in memory tasks was better. In low frequency bands, FC was negatively associated with attentional, memory, and problem-solving abilities. Within higher bands instead, FC was positively related to tasks assessing working-memory and memory.

4.1.1 Functional Differences between Patients and Controls

The comparison between healthy controls and GGE patients revealed an increased FC and power in patients. For CohImg this was observed only in low frequencies (delta, theta, and alpha) while for power it became significant over all frequency bands. Emphasis of differences lay in frontal, temporal, and parietal regions.

Results correspond to the findings of Stier et al. (2021), who reported an increased FC and power for the same GGE patients as described here, but who used source-reconstruction MEG analysis instead of EEG analysis. Thus, the **first hypothesis**, namely that GGE patients show a higher FC/power compared to healthy controls is supported. This is further in line with reported increases in FC using MEG-source-reconstruction in different samples (Elshahabi et al. 2015; Li Hegner et al. 2018). This conformity of results is evidence of the robustness of the identified effects as the two different procedures showed converging results. While EEG directly measures electrical current due to neuronal activity in the brain, MEG records changes in the magnetic field which are eventually caused by the alterations of the electrical current on the brain (Hansen et al. 2010).

Besides this methodological contribution, the observed increases also depict the potentially underlying physiological mechanism taking place in GGE patients. As described in section 1.1.4, a main aspect of GGE and epilepsy in general is a pathologically synchronous neuronal activity. This elevation of neuronal communication could result in increased functional network activity, as presented in this thesis, and disturb physiological neuronal exchanges (Moshé et al. 2015). However, it is unknown whether such network enhancements are

characteristic of GGE or whether they can be found in other forms of epilepsy as well. Li Hegner et al. (2018) compared FC of patients with focal epilepsy and GGE patients. Both groups showed an increased connectivity in frontal, temporal and parietal regions when compared to healthy controls. However, while such changes were reported for GGE patients in alpha, beta1 and theta, patients with focal epilepsy lacked significant increases in the alpha frequency band. Furthermore, in a subgroup-analysis, GGE patients showed a higher FC in mesio-frontal and motor areas than patients with focal epilepsy (Li Hegner et al. 2018). Similarly, Stier et al. (2021) and this thesis identified increased FC and power in the alpha frequency band. Additionally, both parameters were also increased for the theta frequency band. Together, this indicates an underlying enlarged synchronization of those two frequency bands in GGE. In addition, both frequency bands were found to be increased in another source-reconstruction analysis (Elshahabi et al. 2015). Keeping in mind that patients with focal epilepsy lacked an alpha alteration, the combination of enhanced connectivity in alpha and theta could be specific for GGE and therefore be of potential value for clinical differential diagnosis.

However, Stier and colleagues (2021) found FC to be increased in all but the delta frequency band. This stands in contrast to the findings of this thesis which revealed strong increases of FC in the delta frequency band in GGE-patients. Compellingly, this increase was also not present in other MEG-source-reconstruction works mentioned in the previous section (Elshahabi et al. 2015; Li Hegner et al. 2018), indicating a possible methodological issue. Indeed, as was stressed in section 1.2, although closely related, MEG and EEG are two different modalities measuring different parts of the neuronal signal. While MEG measures only tangential sources, EEG can capture both tangential and radial sources from the brain (Baillet et al. 2001). The difference in delta connectivity could therefore result from MEG simply not being able to record those, assumably primarily radial, neuronal sources which are responsible for a potential increase in delta connectivity. At present, no study exists which analysed FC of GGE patients using EEG and found an increase in delta connectivity. This could, of course, be due to the prevalent dominance of sensor-based connectivity analyses compared to a source-level approach in existing research. It could therefore be assumed that the within reported increase in delta FC was to date not discovered due to insensitive sensor-based analyses and is only now revealed by the more sophisticated source-level approach. The intermediate-to-strong effect sizes of results obtained herein argue for a low likelihood of a mere false positive. Moreover, Stier et al. (2021) reported increases for delta, albeit only in terms of its power, in line with other investigations (Elshahabi et al. 2015), including one using EEG (Clemens et al. 2011). It can thus be inferred that differences in power do not

represent connectivity changes. In addition, CohImg only shows phase-shifted connectivity, while power reflects only differences in amplitude. Thus power should not affect connectivity substantially (Elshahabi et al. 2015).

4.1.2 Influence of Clinical Variables

For the **second hypothesis**, three clinical variables were investigated to determine whether and how they could influence FC/power of EEG in GGE patients: existence of GSWDs in EEG recordings, reported seizures within the last 12 months and number of AEDs.

Patients who showed GSWDs in the recorded EEG data had a significantly increased FC in delta and gamma. The strongest effects were found in the supramarginal gyrus. These results are partially in line with Stier et al. (2021) who also reported an intensified FC in delta. Thus, **hypothesis 2a**, which assumed an increased FC/power for patients with GSWDs in EEG recordings, can be supported only to a limited extent. Although the actual GSWDs were excluded from analysis including 10 s before and after the respective event, patients with GSWDs still showed an increased FC. This could indicate a possible enforcement of hypersynchronous neuronal activity for patients who show interictal GSWD patterns. Thus, such patients could be more prone to develop seizures, as their basic connectivity level seems to be higher. It could also support the idea that GSWD's development occurs over a larger period of time and does not start abruptly but rather shows a dynamic evolution in network connectivity before the actual (visible) GSWD (Tangwiriyasakul et al. 2018). Consequently, the found increase could simply be due to GSWDs changing the focal signal into a stronger, more powerful EEG pattern.

It is assumed that GSWDs originate from cortical areas and then pass through the thalamus (Meeren et al. 2005). Perhaps the supramarginal gyrus serves as a starting point for these patterns. Moreover, the supramarginal gyrus is an area known to be involved in social and emotional processing (Olson et al. 2007). To date FC for this area has been reported decreased in GGE patients when compared to healthy controls using fMRI, a circumstance that is associated with a lack of empathy and increase of impulsivity found in some patients with GGE (Camfield and Camfield 2010; Ji et al. 2014). Based on the data presented in this thesis, one could speculate that interictal GSWDs are involved with social skills by increased FC of the supramarginal gyrus. To answer this question research which properly investigated social skills in GGE patients with and without GSWDs, for instance, by using a social cognition test battery would be necessary (Tousignant et al. 2017). Regardless of this idea, it is

noteworthy that the group of patients with GSWDs was small, thereby limiting statistical power.

Patients who had seizures within 12 months prior to the investigation showed a decreased power in alpha, beta1, beta2 and gamma. No significant differences were found in CohImg. This pattern was unexpected and thus does not support **hypothesis 2b**, which proposed a lack of change in FC/power depending on recent seizures. A seizure is the result of hypersynchronous neuronal activity. Furthermore, the risk of having a subsequent seizure is highest within one to two years after a seizure (Krumholz et al. 2015). Therefore, one could assume that recent seizures, if at all, would have a reinforcing effect on the patient's brain activity and hence connectivity/power increasing the risk for seizure reoccurrence. Potential sex bias may be one reason why a different pattern was found. A recent study by Cave and Barry (2021) showed that healthy women have a higher overall EEG-amplitude at the sensor level in delta, alpha and beta frequency bands than men. In the herein reported sample, the patient group without seizures in the previous 12 months consisted mostly of women (n_{women} = 11, n_{men} = 5), whereas in the other group the majority was made up of men (n_{women} = 3, n_{men} = 6). Hence, the overwhelming portion of women in the first group could have confounded the underlying actual effect. As men showed a higher signal power than women however, this argument does not seem tenable. Perhaps the interaction between water-based EEG and the larger amount of hair on women's heads plays a role. While the within analysis accounted for potential sex effects, according to Field et al. (2012) simply adding a covariate such as sex into a model does not balance out its potential influence completely. Despite analysing the same sample, Stier et al. (2021) found no significant associations between recent seizures and MEG connectivity/power, suggesting a lack of influence of the respective variable. Future research using a more properly balanced patient group would be of interest to further investigate this matter.

In terms of the association between AEDs and FC/power, patients who used two or more AEDs at the time of investigation showed a weaker FC in delta than those with fewer. Thus, the expected pattern of decreased FC/power in patients with two or more AEDs, as postulated in **hypothesis 2c**, is partly supported. The strongest effects were found in the right superior temporal cortex. On the left hemisphere, this region has been identified to be structurally altered in GGE patients. Betting and colleagues (2010) reported grey matter abnormalities in the left superior temporal gyrus in absence patients. Furthermore, its cerebral blood flow was found to be increased in GGE patients suggesting a cortical dysfunction in the temporal region and a potential connection to epileptic activity (Chen et al. 2016).

Treatment effects of AEDs might thus partly work through down-regulation of neuronal activity in temporal regions. Moreover, while the mere direction of the effects reported in this thesis was similar to Stier et al. (2021), they identified only beta1 to be significantly decreased. Nonetheless, the direction of effects suggests that AEDs reduce network connectivity. This is supported by findings of Ricci and colleagues (2021) who found AED therapy to decrease connectivity in temporal lobe epilepsy using EEG-data. Thus, it is possible that AEDs disrupt the networks responsible for seizure generation resulting in a collapse of synchronizing neuronal activity (Ricci et al. 2021). Nevertheless, no consensus exists about the associations between AEDs and FC in general. Under treatment with Eslicarbazepine connectivity was found to be increased in all frequency bands in patients with temporal lobe epilepsy (Pellegrino et al. 2018). The ambivalence is understandable, as the variety of AEDs is large and pathophysiological effects are diverse (see section 1.1.6 for more details). For treating absences Ethosuximide enforces the activity of GABA-ergic inhibitory neurons while Valproic acid inhibits ion channel function (e. g. sodium channels) and results in reduction of the neurotransmitter glutamate. It would surely be of interest to more thoroughly investigate how the correlations with connectivity differ between single AEDs. Despite differences in the direction of effects, a common finding is the normalization of connectivity and power in patients with epilepsy (Arzy et al. 2010; Clemens et al. 2014; Pellegrino et al. 2018; Ricci et al. 2021).

All-in-all, the second hypothesis which aimed at substantiation of the effects of clinical variables found by Stier et al. (2021) could be partly supported. While results were similar for GSWDs in the EEG recording and for the usage of AEDs, significant differences were identified in power for patients with seizures in the last 12 months.

4.1.3 Association with Neurophysiological Parameters

A simple comparison of cognitive performance revealed significant deviations from the norm sample within the patient group, for example in tests for memory, intelligence, problem solving and mood. However, only performance in the figural learning and memory test survived conservative correction, suggesting memory to be a key component affected in GGE patients. In line with this notion, patients with epilepsy complain most frequently about having memory problems (Hamed 2009). Research has already demonstrated a decrease in memory skills of GGE patients compared to healthy controls (Davidson et al. 2007; Wandschneider et al. 2010; Grayson-Collins et al. 2017). Nevertheless, it is still not clear which factors influence the cognitive performance within the GGE cohort. Dickson (2006)

suggests a potentially underlying correlation between memory abilities and temporal lobe dysfunction leading to differences within the patient cohort. However, the argument of memory impairment is debatable as Muhlert et al. (2011) observed memory differences in temporal lobe epilepsy but not in GGE and a more recent review came to the conclusion that memory might not be a specific marker for GGE in general (Ratcliffe et al. 2020).

One reason for cognitive differences within the patient cohort could be the use of AEDs as they have been linked in some studies to worsened memory performance in epilepsy patients (Motamedi and Meador 2004; Quon et al. 2020). The **third hypothesis** of this thesis predicted a worsened cognitive performance under AED polytherapy. However, actual results revealed a diverse pattern. On the one hand patients who took fewer AEDs showed a better performance in attention and executive functioning than those who took more. On the other hand, this pattern was inverted regarding verbal memory performance. Furthermore, taking global FC/power into account, the main trend of medication effects was still present. An improvement in cognition when AEDs are lower in number is in line with current research, which shows a decline in cognitive performance with increasing number of currently used AEDs (Quon et al. 2020). The mechanisms underlying this pattern are not understood completely. However, their effect is believed to occur due to modulations of neurotransmitter levels, such as GABA, glutamate and acetylcholine (Kundap et al. 2017). Other reasons should be considered as well. Firstly, the difference between patients receiving more than one AED compared to patients receiving fewer than two AEDs could be driven by patients not taking any AEDs disproportionally, as their cognition remains presumably unaffected. But since only two subjects had no AED usage at the time of investigation, this explanation seems unrealistic. Secondly, it could also be possible that a current monotherapy improves patients' cognitive performance through better seizure control. As an example, Cho et al. (2012) showed an improvement in patients' cognitive performance under monotherapy with Levetiracetam. However, the patient sample consisted of patients with GGE and focal epilepsies. A possible differentiating effect of the underlying epilepsy subsyndrome can thus not be excluded. Nevertheless, this second line of reasoning could explain the better performance found in executive functioning (Gavrilovic et al. 2019). An improved performance under AED polytherapy especially in memory tasks is, however, contradictory to current research establishing an impairing effect (Quon et al. 2020). An explanation for the identified pattern could lie in the already existing memory deficits observed in GGE patients (Dickson 2006). Perhaps these deficits are so persistent that a combination of AEDs is necessary or more effective in improving such features than is a single or no AED treatment at all. It is noteworthy that none of the reported results survived Bonferroni correction. Effects of AEDs

on cognition were either very weak or non-existent. While research is different for AEDs in general, the latter could be the effect of certain drugs distorting results (Quon et al. 2020). In studies with Gabapentin or Lamotrigine no significant differences in cognitive performance were found when compared to placebo groups (Leach et al. 1997; Placidi et al. 2000). Furthermore, not all AEDs follow the same neuropathological mechanisms and therefore their effects on cognitive performance could be significantly different.

But perhaps the differences in cognition are also influenced by functional neuronal parameters, such as FC or power. Therefore, the last goal of this thesis was to explore the relation between these parameters and neuropsychological test scores. The association between FC/power and cognitive performance revealed two patterns. In lower frequency bands, increases in FC and power were mostly associated with a decrease in cognitive performance such as attention, verbal memory, and problem-solving. This order was inverted in higher frequency bands, indicating a better performance for higher FC/power measures. To better understand this constellation, it is helpful to remember the results from the patient-control comparison (see section 3.1.1). GGE patients showed a significant increase in FC and power respectively compared to healthy controls. While this was the case for all frequencies in power analysis, for FC it was only found to be significant in the three lower frequency bands, namely delta, theta, and alpha. These are also the frequency bands in which better cognitive performance was mainly associated with a decrease in FC/power. It could therefore be assumed that as connectivity is pathologically increased in these frequency bands, cognitive performance is impaired. A lower connectivity in those frequencies is closer to the normal neuronal dynamics observed in healthy controls and associated with a regular cognitive performance. Connectivity in the higher frequency bands (beta1, beta2 and gamma) was within normal ("healthy") range and for them cognitive performance was better when FC/power was increased. This is consistent with the finding that EEG-FC positively correlates with cognitive performance in several frequency bands in healthy subjects, including theta, alpha, and gamma (Finnigan and Robertson 2011; Langer et al. 2012; Vecchio et al. 2016). Moreover, in a structural analysis Ystad et al. (2011) reported a positive correlation between white matter integrity and performance in executive functions and processing speed of healthy subjects. Also, in the here-introduced data two significant regression coefficients survived corrections for multiple comparisons, indicating a strong positive association between FC and cognitive performance in the high frequency bands of GGE patients as well. To sum up the here mentioned idea, cognition and FC/power are negatively associated when FC is significantly higher (and perhaps pathological) than those of healthy controls (low frequency bands in this sample) and positively associated when FC is similar to those of healthy controls

(high frequency bands in this sample).

Yet another explanation for the relation between FC/power and cognitive performance would be possible. Wei et al. (2016) reported an association between reduced fMRI-connectivity and cognitive dysfunction in GGE. The authors argued that the FC in GGE patients is disrupted resulting in impaired cognition. Because in the sample used herein, GGE patients were shown to have increased FC in lower and comparably normal connectivity in the higher frequencies when compared to healthy controls, this explanation must be questioned. Of course, it is possible that potential differences between groups were statistically underpowered. Consequently, FC could actually be lower in higher frequencies of GGE patients as well. While a disruption in GGE patients can be an explanation, data from this thesis suggest otherwise. It is possible that the mechanisms of the link between FC and cognition differ depending on the subject group. To speculate, controls could rely on an improvement of neuronal connections resulting in faster and more efficient neuronal responses. GGE patients' connectivity networks instead were altered leading to a different, maybe even less efficient, neuronal response. Unfortunately, no data on cognitive performance was available for the healthy controls to check for possible differences in associations between FC/power and cognition. Therefore, possible differences can only be assumed.

All-in-all, the associations among FC/power, AEDs and neuropsychological tests in our study need further investigation. Other factors are likely to influence cognition which were not considered in this analysis, such as GGE-subsyndromes (Chowdhury et al. 2014a), social status and comorbid psychiatric disorders (Elixhauser et al. 1999; Kimiskidis et al. 2007; Kundap et al. 2017). Based on only those effects that persist after Bonferroni correction (and are thus relatively large in nature), the following conclusions can be drawn. First, no significant associations between AEDs and cognitive performance of the patients were found. Second, a higher FC in patients with GGE is associated with a better performance in verbal memory and working memory tasks respectively.

4.1.4 Strengths

The main advantage of this investigation is that connectivity data have been acquired twice for the same sample with the only difference being the device used for recording the neuronal signal. A strict methodological comparison was hence possible. Although outcomes were not identical between EEG and MEG, they showed a comparable direction indicating a consistent pathology in GGE. In contrast to the indirect measurements of neuronal activity obtained with fMRI, EEG and MEG both capture brain activity directly (Stam and van Straaten 2012). While MEG and EEG probably identify closely linked neuronal processes, it is

indicated that they measure different parts of the neuronal signal. In contrast to EEG, MEG is unable to record signals from radial neuronal sources in the brain (Baillet et al. 2001). That is to say, this EEG-analysis added more information about the pathophysiological patterns underlying GGE.

Moreover, signal quality of MEG and EEG is affected by the problem of volume conduction (see section 1.3 for further details; Winter et al. 2007). To account for this issue, another positive feature utilized herein is the application of source-connectivity analysis by using individual head model, a rigorous yet rarely applied approach addressing connectivity in GGE patients (Stier et al. 2021). In order to minimize the effects of volume conduction a statistical approach, called the imaginary part of coherency (Nolte et al. 2004), which precludes perfect coherence values and thus enables to properly capture brain interactions, was used.

Although the herein reported sample is not particularly large (n = 25), multiple effects survived conservative corrections, suggesting relatively strong effects. This study also took cognition into account. While cognitive dysfunction in GGE is a commonly investigated topic, combining it with connectivity analyses, especially based on source-based EEG data, is scarce.

4.1.5 Limitations

The sample-sizes for subgroup-analyses of clinical variables in the patient group were small, limiting power of results. A more extensive sample might further clarify possible effects.

While CohImg is said to be more resistant to the problem of volume conduction than other FC measures, it is not a perfect measurement for connectivity investigations. It has reportedly poor test-retest reliability, which is why some argue for using the signal amplitude instead (Colclough et al. 2016). A problem with CohImg is that it excludes all perfect coherences. On the one hand, this reduces spurious connectivity due to recording of the same sources. On the other hand, the existence of moments with perfect coherence in neuronal activity has been defended (Gollo et al. 2014), resulting in a possible exclusion of meaningful physiological data by CohImg. Specifically tailored methodological solutions would allow for focusing on perfect coherence in future work (Hauk and Stenroos 2014; Colclough et al. 2016).

Although significant effects were found for the influence of AEDs and seizures, the variables representing these features are categorial and not continuous. Reality is more complex and richer in information than answering "yes" or "no" to having had seizures in the past 12 months. Therefore, these variables lack detailed information about the actual underlying associations, limiting statistical power. Furthermore, although the specific type of AED and its

amount were noted, information was too diverse to create reasonably powered subgroups from it. Thus, it is unclear which specific drugs and corresponding dosages improve or worsen FC/power or even cognition respectively.

Unlike for age and sex, participants were not matched for educational differences. However, such a match could have been of value as years of education were observed to have a significant effect on structural and FC in healthy subjects (Arenaza-Urquijo et al. 2013). Education was also found to have a protective effect on cognitive performance, especially on memory (Schneeweis et al. 2014). Thus, the observed differences in memory tests could simply be associated with differences in years of education or intelligence.

Unfortunately, no data on cognition was available for the control group. GGE patients are observed to perform slightly worse than healthy subjects but still within normal range. Without a reference group this could not be further explored.

Lastly, it needs to be mentioned that this study was part of a large investigation lasting five to six hours. Before neuropsychology was assessed, subjects had already spent about 90 minutes being analysed by EEG and MEG. It is possible that cognitive performance along with concentration were already affected by the research time.

4.1.6 Implications for Future Research

This study found significant increases of power and FC for GGE patients compared to controls. A closer look into the different GGE-subsyndromes could lead to a more differentiated view on connectivity differences within patient cohorts as research on the topic is, at present, ambivalent (Chowdhury et al. 2014a; Focke et al. 2014; Kim et al. 2014; Li et al. 2017). Li et al. (2017), for instance, found a significant difference in fMRI-connectivity between patients with myoclonic and with absence seizures respectively. Compared to healthy controls, patients with myoclonic seizures showed increased FC, whereas FC was decreased for those with absence seizures. Furthermore, contrary to other GGE-subsyndromes, CAE patients showed no impairments in a cognitive task for verbal fluency (Chowdhury et al. 2014a). But according to other studies, no structural or functional differences exist between GGE subsyndromes (Focke et al. 2014; Kim et al. 2014). Even in terms of distinct cognitive profiles, no significant patterns were found (Loughman et al. 2014; Ratcliffe et al. 2020). All studies reviewed provide conflicting evidence. Additional research on differences within the GGE cohort could further the understanding of the disease itself. Are the subsyndromes only part of a large GGE continuum or are they more distinctly separated from each other? A study by Marini et al. (2004), for instance, described an underlying genetic relationship between

CAE and JAE but found a more distinct genetic pattern for JME. However, as GGE's aetiology is understood as being polygenic, further exploration of differences and similarities between the subsyndromes would be of significant interest to improve understanding of the pathophysiology (Koeleman 2018). Consequently, this study could be repeated with a larger sample-size of patients with GGE-subsyndromes.

Furthermore, the differences between patients and controls could improve the development of potential biomarkers for the detection of the disease. This study used two parameters to assess brain oscillations, namely CohImg and power. Comparison between GGE patients and controls revealed differing results for both with power showing much stronger effects spread over all frequency bands. Also, emphasis of differences in power was over temporo-frontal regions whereas CohImg demonstrated its strongest effects over temporo-parietal regions. Accordingly, the actual parameters used may capture features that are somewhat independent from each other. As next steps, other parameters besides CohImg and power could be incorporated into the analysis. No perfect measure for FC exists, and it would be therefore helpful for future studies to compare the several metrics and scrutinize their reproducibility and similarity of patterns.

One problem of including such patterns into day-to-day medical routine is the HD-EEG used herein or even the MEG included by Stier et al. (2021). While both are available in larger hospitals, due to their high costs they are scarce among smaller ones or even among practitioners that are not affiliated with hospitals. An HD-EEG, for instance, can cost about $75,000, an MEG about $2 million (Biosemi 2021; Schwindt 2014). Wide application of these results would likely require an investigation into whether similar results are yielded by a much cheaper, and hence easier to acquire, routine EEG system with only 16 or 32 channels.

In addition, integrating detailed information about the seizure type that occurred and the exact date of the seizure into analysis would be valuable. It may be that absences have a different effect on connectivity as do myoclonic seizures. Perhaps it also makes a difference to the measured connectivity networks if a seizure has happened a month, as compared to eleven months, previous. However, it is hard to form subgroups based on this. Sometimes a patient cannot remember their last seizure or possibly did not notice it. To investigate these variables properly, one would need to assess them systematically, by using a diary for instance.

Further, pharmaceutical effects on connectivity and cognition remain to be investigated more thoroughly. This study only used the number of AEDs taken by patients as a predictor, thus

following a categorial approach. Future research could focus on the specific type of AED as well as the exact dosage to analyse data using continuous variables and possible moderating effects. While the effect of AEDs on cognition did not survive correction for multiple comparisons, a potential influence could still exist. Topiramate, for instance, has been repeatedly shown to impair cognition, mainly language skills. This relationship is, however, dose-dependent and appeared in about 10 % of patients under Topiramate treatment (Mula 2012). Effects on cognition could have severe consequences as GGE can become manifest at an early age and can consequently cause difficulties in school or later job performance. In line with this, a larger study sample would surely help to enforce effect strength and improve clarity of results.

It would also be interesting to compare interactions of FC/power and cognitive performance between patients and controls. Hence, future research should include neuropsychological assessment for the control group and make use of a more standardised scheme for neuropsychological testing (e. g. as introduced by Brückner 2012). So far, studies investigating cognition in GGE have used inconsistent tests thereby limiting the comparability of their findings. A coherent cognitive test battery for GGE patients which, for instance, includes tests about memory or executive functioning and ultimately allows the creation of cumulative knowledge is due. A similar approach has been applied in the analysis of cognitive dysfunction of patients with Amyotrophic Lateral Sclerosis, a neurodegenerative disease. In this case the Edinburgh Cognitive and Behavioural ALS Screen is beginning to succeed in establishing the same standard internationally (Abrahams et al. 2014).

4.1.7 Conclusion

This study investigated the functional changes in patients with GGE and how they differed in comparison to healthy controls. Furthermore, it analysed the influence on clinical variables on FC, such as AEDs, GSWDs in recordings and recent seizures. Results were compared to the analysis by Stier et al. (2021) who examined the same cohort, but using MEG instead of HD-EEG. Lastly, it focussed on the association between cognitive performance, FC, and use of AEDs.

GGE patients showed an increased FC and power bilaterally and across several brain regions compared to healthy controls, supporting previous research, and emphasizing the theory of hypersynchronous neuronal activity underlying pathophysiological mechanisms in GGE. It is possible that this difference can one day serve as a biomarker to identify such patients.

Additionally, more information about the distinct patterns in the GGE subsyndromes might be the basis for easier and more accurate diagnoses in the future.

However, next to this increased FC/power, clinical factors seem to moderate these changes. We assume that AEDs have a suppressive effect on FC whereas the presence of interictal GSWDs enforces it. This interpretation gains methodological support through similar findings by Stier et al. (2021). However, as the causality of found effects is unclear, this interpretation remains an assumption and calls out for more thorough investigations.

Cognitive performance differed significantly within the GGE patient sample. This interindividual variability might have been influenced by factors such as GGE subsyndrome or social status. Also, medication might impact cognition and connectivity levels. Future research should systematically assess the contributions made by each. In this thesis however, a positive association was found between connectivity levels and cognitive performance, indicating a potential "protective effect" of connectivity on cognitive aspects, foremost working memory and verbal memory. This emphasizes the importance of considering such features when assessing neuropsychological abilities in patients.

All-in-all, this investigation provides additional evidence to enhance the understanding of functional changes occurring in GGE-patients, eventually supporting the improvement of diagnostical features, treatment, and long-term care of patients.

5 Summary

Genetic generalized epilepsy makes up about a third of all epileptic syndromes. While its aetiology is believed to mainly result from genetic factors, its pathophysiology remains an enigma to research. A recent study by our research group focused on functional neuronal dynamics of the disease and observed increased functional connectivity and power in patients when compared to healthy controls using magnetoencephalography and a source-level-approach. The goal of this work was to examine the same participants but using electroencephalography instead and explore the association between cognition and functional connectivity/power and anti-epileptic-drugs respectively, within the patient sample.

Twenty-five patients with genetic generalized epilepsy and 40 healthy controls were examined during resting-state using high-definition electroencephalography. Five minutes of cleaned resting-state data were analysed using a source-based approach. Furthermore, patients underwent a neuropsychological test battery.

Analyses revealed an increased functional connectivity/power in patients with genetic generalized epilepsy compared to healthy controls with an emphasis on the theta frequency band. Furthermore, patients who had shown generalized spike-wave-discharges in the recorded electroencephalogram had a higher functional connectivity than those without. Having had seizures in the last 12 months was associated with a reduced power. In addition, a decreased functional connectivity in delta was observed for patients who took two or more anti-epileptic drugs at the time of investigation. Analysis of cognitive profiles revealed frequency-band specific results for the interaction between pharmaceutical treatment and neuropsychological performance. While in lower frequency bands more drugs were associated with better cognitive performance this observation was inverted for higher frequency bands. In high frequency bands (beta2 and gamma), a higher functional connectivity was associated with better cognitive performance in working memory and verbal memory.

Results enforce the idea of a hypersynchronous neuronal activity underlying the pathophysiology in genetic generalized epilepsy and the overlap with previous magnetoencephalography results of the same sample emphasizes robustness of observed effects. Moreover, these changes in functional dynamics are moderated by clinical factors, such as pharmaceutical treatment or pathological electroencephalography-patterns. A possible protective association between functional connectivity and cognition was observed and emphasizes the relevance of potential covariates influencing cognition in patients.

6 Literature

Abrahams S, Newton J, Niven E, Foley J, Bak TH (2014): Screening for cognition and behaviour changes in ALS. Amyotroph Lateral Scler Front Degener 15, 9–14

Aghakhani Y (2004): fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. Brain 127, 1127–1144

Akanuma N, Hara E, Adachi N, Hara K, Koutroumanidis M (2008): Psychiatric comorbidity in adult patients with idiopathic generalized epilepsy. Epilepsy Behav 13, 248–251

Aldenkamp A, Arends J (2004): The Relative Influence of Epileptic EEG Discharges, Short Non-convulsive Seizures, and Type of Epilepsy on Cognitive Function. Epilepsia 45, 54–63

Alexander SP, Catterall WA, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Southan C, et al. (2015): The Concise Guide to Pharmacology 2015/16: Voltage-gated ion channels. Br J Pharmacol 172, 5904–5941

Anastassiou CA, Perin R, Markram H, Koch C (2011): Ephaptic coupling of cortical neurons. Nat Neurosci 14, 217–223

Arenaza-Urquijo EM, Landeau B, La Joie R, Mevel K, Mézenge F, Perrotin A, Desgranges B, Bartrés-Faz D, Eustache F, Chételat G (2013): Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. NeuroImage 83, 450–457

Arzy S, Allali G, Brunet D, Michel CM, Kaplan PW, Seeck M (2010): Antiepileptic drugs modify power of high EEG frequencies and their neural generators. Eur J Neurol 17, 1308–1312

Asadi-Pooya AA, Emami M, Sperling MR (2013): A clinical study of syndromes of idiopathic (genetic) generalized epilepsy. J Neurol Sci 324, 113–117

Ashburner J (2007): A fast diffeomorphic image registration algorithm. NeuroImage 38, 95–113

Ashburner J, Friston KJ (2005): Unified segmentation. NeuroImage 26, 839–851

Baillet S, Mosher JC, Leahy RM (2001): Electromagnetic brain mapping. IEEE Signal Process Mag 18, 14–30

Balestrini S, Arzimanoglou A, Blümcke I, Scheffer IE, Wiebe S, Zelano J, Walker MC (2021): The aetiologies of epilepsy. Epileptic Disord 23, 1–16

Bastos AM, Schoffelen JM (2016): A Tutorial Review of Functional Connectivity Analysis Methods and Their Interpretational Pitfalls. Front Syst Neurosci 9, e00175

Beck AT, Steer RA, Brown GK: Beck-Depressions-Inventar Revision: Deutsche Bearbeitung von M. Hautzinger, F. Keller, C. Kühner. Pearson, München 2009

Benbadis S (2009): The differential diagnosis of epilepsy: A critical review. Epilepsy Behav 15, 15–21

Berg AT, Shinnar S, Levy SR, Testa FM (1999): Newly Diagnosed Epilepsy in Children: Presentation at Diagnosis. Epilepsia 20, 445–452

Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, et al. (2010): Revised terminology and concepts for

organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 51, 676–685

Berger H (1929): Über das Elektroenkephalogramm des Menschen. Arch Psychiatr Nervenkr 87, 527–570

Berkovic SF, Howell RA, Hay DA, Hopper JL (1998): Epilepsies in twins: Genetics of the major epilepsy syndromes. Ann Neurol 43, 435–445

Bernhardt BC, Rozen DA, Worsley KJ, Evans AC, Bernasconi N, Bernasconi A (2009): Thalamo–cortical network pathology in idiopathic generalized epilepsy: Insights from MRI-based morphometric correlation analysis. NeuroImage 46, 373–381

Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, Vaughn BV: The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, Version 2.2. American Academy of Sleep Medicine, Darien, Illinois 2015

Bertram EH (2013): Neuronal circuits in epilepsy: Do they matter? Exp Neurol 244, 67–74

Betjemann JP, Lowenstein DH (2015): Status epilepticus in adults. Lancet Neurol 14, 615–624

Betting LE, Mory SB, Li LM, Lopes-Cendes I, Guerreiro MM, Guerreiro CAM, Cendes F (2006): Voxel-based morphometry in patients with idiopathic generalized epilepsies. NeuroImage 32, 498–502

Betting LE, Li LM, Lopes-Cendes I, Guerreiro MM, Guerreiro CAM, Cendes F (2010): Correlation between quantitative EEG and MRI in idiopathic generalized epilepsy. Hum Brain Mapp 31, 1327–1338

Biervert C (1998): A Potassium Channel Mutation in Neonatal Human Epilepsy. Science 279, 403–406

Biosemi (2021): BioSemi products prices. https://www.biosemi.com/faq/prices.htm; accessed on 06.09.2021

Blume WT, Lemieux JF (1988): Morphology of spikes in spike-and-wave complexes. Electroencephalogr Clin Neurophysiol 69, 508–515

Blumenfeld H (2005): Cellular and Network Mechanisms of Spike-Wave Seizures. Epilepsia 46, 21–33

Bomben VC, Aiba I, Qian J, Mark MD, Herlitze S, Noebels JL (2016): Isolated P/Q Calcium Channel Deletion in Layer VI Corticothalamic Neurons Generates Absence Epilepsy. J Neurosci 36, 405–418

Brickenkamp R, Schmidt-Atzert L, Liepmann D: test d2-revision: Aufmerksamkeits- und Konzentrationstest. Hogrefe, Göttingen 2010

Brodie MJ, Barry SJE, Bamagous GA, Norrie JD, Kwan P (2012): Patterns of treatment response in newly diagnosed epilepsy. Neurology 78, 1548–1554

Brückner K (2012): Standard der neuropsychologischen Testung in der prächirurgischen Epilepsiediagnostik: Stellungnahme der neuropsychologischen DGfE-Kommission. Z Für Epileptol 25, 259–263

Burle B, Spieser L, Roger C, Casini L, Hasbroucq T, Vidal F (2015): Spatial and temporal resolutions of EEG: Is it really black and white? A scalp current density view. Int J Psychophysiol 97, 210–220

Buzsáki G: Rhythms of the Brain. Oxford University Press, Oxford 2006

Cameron A, Bansal A, Dua T, Hill SR, Moshe SL, Mantel-Teeuwisse AK, Saxena S (2012): Mapping the availability, price, and affordability of antiepileptic drugs in 46 countries: Availability, Price, and Affordability of AEDs. Epilepsia 53, 962–969

Camfield P, Camfield C (2010): Idiopathic generalized epilepsy with generalized tonic-clonic seizures (IGE-GTC): A population-based cohort with >20year follow up for medical and social outcome. Epilepsy Behav 18, 61–63

Cave AE, Barry RJ (2021): Sex differences in resting EEG in healthy young adults. Int J Psychophysiol 161, 35–43

Chavez M, Valencia M, Navarro V, Latora V, Martinerie J (2010): Functional Modularity of Background Activities in Normal and Epileptic Brain Networks. Phys Rev Lett 104, e118701

Chen G, Lei D, Ren J, Zuo P, Suo X, Wang DJJ, Wang M, Zhou D, Gong Q (2016): Patterns of postictal cerebral perfusion in idiopathic generalized epilepsy: a multi-delay multi-parametric arterial spin labelling perfusion MRI study. Sci Rep 6, e28867

Chen Y, Lu J, Pan H, Zhang Y, Wu H, Xu K, Liu X, Jiang Y, Bao X, Yao Z, et al. (2003): Association between genetic variation ofCACNA1H and childhood absence epilepsy. Ann Neurol 54, 239–243

Cho JR, Koo DL, Joo EY, Yoon SM, Ju E, Lee J, Kim DY, Hong SB (2012): Effect of levetiracetam monotherapy on background EEG activity and cognition in drug-naïve epilepsy patients. Clin Neurophysiol 123, 883–891

Chowdhury FA, Elwes RDC, Koutroumanidis M, Morris RG, Nashef L, Richardson MP (2014a): Impaired cognitive function in idiopathic generalized epilepsy and unaffected family members: An epilepsy endophenotype. Epilepsia 55, 835–840

Chowdhury FA, Woldman W, FitzGerald THB, Elwes RDC, Nashef L, Terry JR, Richardson MP (2014b): Revealing a Brain Network Endophenotype in Families with Idiopathic Generalised Epilepsy. PLoS One 9, e110136

Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P (2001): De Novo Mutations in the Sodium-Channel Gene SCN1A Cause Severe Myoclonic Epilepsy of Infancy. Am J Hum Genet 68, 1327–1332

Clemens B, Szigeti G, Barta Z (2000): EEG frequency profiles of idiopathic generalised epilepsy syndromes. Epilepsy Res 42, 105–115

Clemens B, Puskás S, Bessenyei M, Emri M, Spisák T, Koselák M, Hollódy K, Fogarasi A, Kondákor I, Füle K, et al. (2011): EEG functional connectivity of the intrahemispheric cortico-cortical network of idiopathic generalized epilepsy. Epilepsy Res 96, 11–23

Clemens B, Puskás S, Besenyei M, Kovács NZS, Spisák T, Kis SA, Emri M, Hollódy K, Fogarasi A, Kondákor I, Fekete I (2014): Valproate treatment normalizes EEG functional connectivity in successfully treated idiopathic generalized epilepsy patients. Epilepsy Res 108, 1896–1903

Cohen J (1992): A power primer. Psychol Bull 112, 155–159

Colclough GL, Woolrich MW, Tewarie PK, Brookes MJ, Quinn AJ, Smith SM (2016): How reliable are MEG resting-state connectivity metrics? NeuroImage 138, 284–293

Commission on Classification and Terminology of the International League (1989): Proposal for Revised Classification of Epilepsies and Epileptic Syndromes. Epilepsia 30, 389–399

Commission on Classification and Terminology of the International League Against Epilepsy, International League Against Epilepsy (1985): Proposal for Classification of Epilepsies and Epileptic Syndromes. Epilepsia 26, 268–278

Davidson M, Dorris L, O'Regan M, Zuberi SM (2007): Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. Epilepsy Behav 11, 394–400

Delgado-Escueta AV, Enrile-Bacsal F (1984): Juvenile myoclonic epilepsy of Janz. Neurology 34, 285–285

Deppe M, Kellinghaus C, Duning T, Moddel G, Mohammadi S, Deppe K, Schiffbauer H, Kugel H, Keller SS, Ringelstein EB, Knecht S (2008): Nerve fiber impairment of anterior thalamocortical circuitry in juvenile myoclonic epilepsy. Neurology 71, 1981–1985

Dibbens LM, Mullen S, Helbig I, Mefford HC, Bayly MA, Bellows S, Leu C, Trucks H, Obermeier T, Wittig M, et al. (2009): Familial and sporadic 15q13.3 microdeletions in idiopathic generalized epilepsy: precedent for disorders with complex inheritance. Hum Mol Genet 18, 3626–3631

Dickson JM (2006): Idiopathic generalised epilepsy: a pilot study of memory and neuronal dysfunction in the temporal lobes, assessed by magnetic resonance spectroscopy. J Neurol Neurosurg Psychiatry 77, 834–840

Drane DL, Meador KJ (2002): Cognitive and behavioral effects of antiepileptic drugs. Epilepsy Behav 3, 49–53

Drury I, Henry TR (1993): Ictal Patterns in Generalized Epilepsy: J Clin Neurophysiol 10, 268–280

Duncan D, John S, Sander JW, Sisodiya SM, Walker MC (2006): Adult epilepsy. The Lancet 367, 1087–100

Elixhauser A, Leidy NK, Meador K, Means E, Willian MK (1999): The relationship between memory performance, perceived cognitive function, and mood in patients with epilepsy. Epilepsy Res 37, 13–24

Elshahabi A, Klamer S, Sahib AK, Lerche H, Braun C, Focke NK (2015): Magnetoencephalography Reveals a Widespread Increase in Network Connectivity in Idiopathic/Genetic Generalized Epilepsy. PLOS One 10, e0138119

Engelborghs S, D'Hooge R, Deyn PPD (2000): Pathophysiology of epilepsy. Acta Neurol Belg 100, 201–213

Field A, Miles J, Field Z: Discovering statistics using R. Sage publication, Thousand Oaks 2012

Finnigan S, Robertson IH (2011): Resting EEG theta power correlates with cognitive performance in healthy older adults. Psychophysiology 48, 1083–1087

Fischl B (2012): FreeSurfer. NeuroImage 62, 774–781

Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J (2005): Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 46, 470–472

Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Forsgren L, French JA, Glynn M, et al. (2014): ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia 55, 475–482

Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, Lagae L, Moshé SL, Peltola J, Roulet Perez E, et al. (2017): Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 58, 522–530

Focke NK, Diederich C, Helms G, Nitsche MA, Lerche H, Paulus W (2014): Idiopathic-generalized epilepsy shows profound white matter diffusion—tensor imaging alterations. Hum Brain Mapp 35, 3332–3342

Fox MD, Greicius M (2010): Clinical applications of resting state functional connectivity. Front Syst Neurosci 4, e00019

Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ (1993): Functional Connectivity: The Principal-Component Analysis of Large (PET) Data Sets. J Cereb Blood Flow Metab 13, 5–14

Gaitatzis A, Sisodiya SM, Sander JW (2012): The somatic comorbidity of epilepsy: A weighty but often unrecognized burden. Epilepsia 53, 1282–1293

Galanopoulou AS, Moshé SL: Neuronal Network Mechanisms—Sex and Development. In: Faingold C, Blumenfeld H (Eds.): Neuronal Networks in Brain Function, CNS Disorders, and Therapeutics. Elsevier, Amsterdam 2014, 145–155

Gaser C, Dahnke R (2016): CAT - A Computational Anatomy Toolbox for the Analysis of Structural MRI Data. Organization for Human Brain Mapping Conference 2016, 336–348

Gastaut H, Gastaut JL, Silva GEG, Sanchez GRF (1975): Relative Frequency of Different Types of Epilepsy: A Study Employing the Classification of the International League Against Epilepsy. Epilepsia 16, 457–461

Gavrilovic A, Toncev G, Boskovic Matic T, Vesic K, Ilic Zivojinovic J, Gavrilovic J (2019): Impact of epilepsy duration, seizure control and EEG abnormalities on cognitive impairment in drug-resistant epilepsy patients. Acta Neurol Belg 119, 403–410

Gesche J, Antonson S, Dreier JW, Christensen J, Beier CP (2021): Social outcome and psychiatric comorbidity of generalized epilepsies – A case-control study. Epilepsia 62, 1158–1169

Gollo LL, Mirasso C, Sporns O, Breakspear M (2014): Mechanisms of Zero-Lag Synchronization in Cortical Motifs. PLoS Comput Biol 10, e1003548

Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F (2005): Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. Proc Natl Acad Sci 102, 15236–15240

Grayson-Collins J, Gascoigne MB, Barton B, Webster R, Gill D, Lah S (2017): Longitudinal study of accelerated long-term forgetting in children with genetic generalized epilepsy: Evidence of ongoing deficits. Cortex 110, 5–15

Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R (2001): Dynamic imaging of coherent sources: Studying neural interactions in the human brain. Proc Natl Acad Sci 98, 694–699

Hacke W, Poeck K, Bendszus M: Neurologie (Springer-Lehrbuch). 13., vollst. überarb. Aufl; Springer Medizin Verlag, Heidelberg 2010

Hamandi K, Salek-Haddadi A, Laufs H, Liston A, Friston K, Fish DR, Duncan JS, Lemieux L (2006): EEG–fMRI of idiopathic and secondarily generalized epilepsies. NeuroImage 31, 1700–1710

Hamed SA (2009): The Aspects and Mechanisms of Cognitive Alterations in Epilepsy: The Role of Antiepileptic Medications. CNS Neurosci Ther 15, 134–156

Hansen P, Kringelbach M, Salmelin R: MEG: An Introduction to Methods. Oxford University Press, Oxford 2010

Haufe S, Nikulin VV, Müller KR, Nolte G (2013): A critical assessment of connectivity measures for EEG data: A simulation study. NeuroImage 64, 120–133

Hauk O, Stenroos M (2014): A framework for the design of flexible cross-talk functions for spatial filtering of EEG/MEG data: DeFleCT. Hum Brain Mapp 35, 1642–1653

Helbig I (2015): Genetic Causes of Generalized Epilepsies. Semin Neurol 35, 288–292

Helbig I, Mefford HC, Sharp AJ, Guipponi M, Fichera M, Franke A, Muhle H, de Kovel C, Baker C, von Spiczak S, et al. (2009): 15q13.3 microdeletions increase risk of idiopathic generalized epilepsy. Nat Genet 41, 160–162

Helmstaedter C, Durwen HF (1990): VLMT: Verbaler Lern- und Merkfähigkeitstest: Ein praktikables und differenziertes Instrumentarium zur Prüfung der verbalen Gedächtnisleistungen. Schweiz Arch Neurol Neurochir Psychiatr 141, 21–30

Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, Walczak TS, Beghi E, Brodie MJ, Hauser WA, for the ILAE Commission on Epidemiology; Subcommission on Mortality (2012a): Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia 53, 249–252

Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA (2012b): Epilepsy, suicidality, and psychiatric disorders: A bidirectional association. Ann Neurol 72, 184–191

Holmes GL, McKeever M, Adamson M (1987): Absence seizures in children: Clinical and electroencephalographic features. Ann Neurol 21, 268–273

Hrachovy RA, Frost JD (2006): The EEG in Selected Generalized Seizures. J Clin Neurophysiol 23, 312–332

Huang W, Lu G, Zhang Z, Zhong Y, Wang Z, Yuan C, Jiao Q, Qian Z, Tan Q, Chen G, et al. (2011): Gray-matter volume reduction in the thalamus and frontal lobe in epileptic patients with generalized tonic-clonic seizures. J Neuroradiol 38, 298–303

Ijff DM, Aldenkamp AP (2013): Cognitive side-effects of antiepileptic drugs in children. Handb Clin Neurol 111, 707–718

Jackson AF, Bolger DJ (2014): The neurophysiological bases of EEG and EEG measurement: A review for the rest of us: Neurophysiological bases of EEG. Psychophysiology 51, 1061–1071

Jackson DC, Dabbs K, Walker NM, Jones JE, Hsu DA, Stafstrom CE, Seidenberg M, Hermann BP (2013): The Neuropsychological and Academic Substrate of New/Recent-Onset Epilepsies. J Pediatr 162, 1047–1053

Jallon P, Latour P (2005): Epidemiology of Idiopathic Generalized Epilepsies. Epilepsia 46, 10–14

Jallon P, Louseau P, Louseau J (2001): Newly Diagnosed Unprovoked Epileptic Seizures: Presentation at Diagnosis in CAROLE Study. Epilepsia 42, 464–475

Janz D: The psychiatry of idiopathic generalized epilepsy. In: Trimble MR, Schmitz, B. (Eds.): The neuropsychiatry of epilepsy. Cambridge University Press, Cambridge 2011, 41–61

Jeong MH, Yum M-S, Ko T-S, You SJ, Lee EH, Yoo HK (2011): Neuropsychological status of children with newly diagnosed idiopathic childhood epilepsy. Brain Dev 33, 666–671

Ji GJ, Zhang Z, Xu Q, Zang YF, Liao W, Lu G (2014): Generalized Tonic-Clonic Seizures: Aberrant Interhemispheric Functional and Anatomical Connectivity. Radiology 271, 839–847

Jokeit H, Ebner A (1999): Long term effects of refractory temporal lobe epilepsy on cognitive abilities: a cross sectional study. J Neurol Neurosurg Psychiatry 67, 44–50

Joober R, Boksa P (2008): A new wave in the genetics of psychiatric disorders: the copy number variant tsunami. J Psychiatry Neurosci 34, 55–59

Kane N, Acharya J, Beniczky S, Caboclo L, Finnigan S, Kaplan PW, Shibasaki H, Pressler R, van Putten MJAM (2017): A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. Clin Neurophysiol Pract 2, 170–185

Kaur J, Kaur A (2015): A review on analysis of EEG signals. International Conference on Advances in Computer Engineering and Applications 2015, 957-960

Killory BD, Bai X, Negishi M, Vega C, Spann MN, Vestal M, Guo J, Berman R, Danielson N, Trejo J, et al. (2011): Impaired attention and network connectivity in childhood absence epilepsy. NeuroImage 56, 2209–2217

Kim JB, Suh S, Seo WK, Oh K, Koh SB, Kim JH (2014): Altered thalamocortical functional connectivity in idiopathic generalized epilepsy. Epilepsia 55, 592–600

Kimiskidis VK, Triantafyllou NI, Kararizou E, Gatzonis SS, Fountoulakis KN, Siatouni A, Loucaidis P, Pseftogianni D, Vlaikidis N, Kaprinis GS (2007): Depression and anxiety in epilepsy: the association with demographic and seizure-related variables. Ann Gen Psychiatry 6, 1–8

Kjeldsen MJ, Kyvik KO, Christensen K, Friis ML (2001): Genetic and environmental factors in epilepsy: a population-based study of 11 900 Danish twin pairs. Epilepsy Res 44, 167–178

Klass DW, Westmoreland BF (1985): Nonepileptogenic epileptiform electroencephalographic activity. Ann Neurol 18, 627–635

Koeleman BPC (2018): What do genetic studies tell us about the heritable basis of common epilepsy? Polygenic or complex epilepsy? Neurosci Lett 667, 10–16

Krumholz A, Wiebe S, Gronseth GS, Gloss DS, Sanchez AM, Kabir AA, Liferidge AT, Martello JP, Kanner AM, Shinnar S, et al. (2015): Evidence-Based Guideline: Management of an Unprovoked First Seizure in Adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsy Curr 15, 144–152

Kundap UP, Kumari Y, Othman I, Shaikh Mohd F (2017): Zebrafish as a Model for Epilepsy-Induced Cognitive Dysfunction: A Pharmacological, Biochemical and Behavioral Approach. Front Pharmacol 8, e00515

Kwan P (2004): The natural history of epilepsy: an epidemiological view. J Neurol Neurosurg Psychiatry 75, 1376–1381

Langer N, Pedroni A, Gianotti LRR, Hänggi J, Knoch D, Jäncke L (2012): Functional brain network efficiency predicts intelligence. Hum Brain Mapp 33, 1393–1406

Leach JP, Girvan J, Paul A, Brodie MJ (1997): Gabapentin and cognition: a double blind, dose ranging, placebo controlled study in refractory epilepsy. J Neurol Neurosurg Psychiatry 62, 372–376

Lee H, Park KM (2019): Structural and functional connectivity in newly diagnosed juvenile myoclonic epilepsy. Acta Neurol Scand 139, 469–475

Lehmann D, Michel CM (1989): Intracerebral dipole sources of EEG FFT power maps. Brain Topogr 2, 155–164

Lehrl S: Mehrfachwahl-Wortschatz-Intelligenztest. Spitta, Balingen 2005

Li Hegner Y, Marquetand J, Elshahabi A, Klamer S, Lerche H, Braun C, Focke NK (2018): Increased Functional MEG Connectivity as a Hallmark of MRI-Negative Focal and Generalized Epilepsy. Brain Topogr 31, 863–874

Li Q, Chen Y, Wei Y, Chen S, Ma L, He Z, Chen Z (2017): Functional Network Connectivity Patterns between Idiopathic Generalized Epilepsy with Myoclonic and Absence Seizures. Front Comput Neurosci 11, e00038

Li Y, Du H, Xie B, Wu N, Wang J, Wu G, Feng H, Jiang T (2010): Cerebellum Abnormalities in Idiopathic Generalized Epilepsy with Generalized Tonic-Clonic Seizures Revealed by Diffusion Tensor Imaging. PLoS ONE 5, e15219

Logroscino G, Hesdorffer DC, Cascino G, Hauser WA, Coeytaux A, Galobardes B, Morabia A, Jallon P (2005): Mortality after a First Episode of Status Epilepticus in the United States and Europe. Epilepsia 46, 46–48

Loring DW, Meador KJ (2004): Cognitive and Behavioral Effects of Epilepsy Treatment. Epilepsia 42, 24–32

Loughman A, Bowden SC, D'Souza W (2014): Cognitive functioning in idiopathic generalised epilepsies: A systematic review and meta-analysis. Neurosci Biobehav Rev 43, 20–34

Marini C, Scheffer IE, Crossland KM, Grinton BE, Phillips FL, McMahon JM, Turner SJ, Dean JT, Kivity S, Mazarib A, et al. (2004): Genetic Architecture of Idiopathic Generalized Epilepsy: Clinical Genetic Analysis of 55 Multiplex Families. Epilepsia 45, 467–478

Meeren H, van Luijtelaar G, Lopes da Silva F, Coenen A (2005): Evolving Concepts on the Pathophysiology of Absence Seizures: The Cortical Focus Theory. Arch Neurol 62, 371–376

Mefford HC, Eichler EE (2009): Duplication hotspots, rare genomic disorders, and common disease. Curr Opin Genet Dev 19, 196–204

Michel CM, Murray MM, Lantz G, Gonzalez S, Spinelli L, Grave de Peralta R (2004): EEG source imaging. Clin Neurophysiol 115, 2195–2222

Moeller F, Maneshi M, Pittau F, Gholipour T, Bellec P, Dubeau F, Grova C, Gotman J (2011): Functional connectivity in patients with idiopathic generalized epilepsy. Epilepsia 52, 515–522

Moorhouse FJ, Cornell S, Gerstl L, Tacke M, Roser T, Heinen F, Bonfert M, von Stülpnagel C, Wagner M, Borggraefe I (2020): Cognitive performance and behavior across idiopathic/genetic epilepsies in children and adolescents. Sci Rep 10, e78218

Moshé SL, Perucca E, Ryvlin P, Tomson T (2015): Epilepsy: new advances. The Lancet 385, 884–898

Motamedi GK, Meador KJ (2003): Epilepsy and cognition. Epilepsy Behav 4, 25–38

Motamedi GK, Meador KJ (2004): Antiepileptic drugs and memory. Epilepsy Behav 5, 435–439

Muhlert N, Grünewald RA, Hunkin NM, Reuber M, Howell S, Reynders H, Isaac CL (2011): Accelerated long-term forgetting in temporal lobe but not idiopathic generalised epilepsy. Neuropsychologia 49, 2417–2426

Mula M (2012): Topiramate and cognitive impairment: evidence and clinical implications. Ther Adv Drug Saf 3, 279–289

Mullen SA, Berkovic SF, the ILAE Genetics Commission (2018): Genetic generalized epilepsies. Epilepsia 59, 1148–1153

Mullins GM, O'Sullivan SS, Neligan A, McCarthy A, McNamara B, Galvin RJ, Sweeney BJ (2007): A study of idiopathic generalised epilepsy in an Irish population. Seizure 16, 204–210

Murthy JMK, Yangala R, Srinivas M (1998): The Syndromic Classification of the International League Against Epilepsy: A Hospital-Based Study from South India. Epilepsia 39, 48–54

Nashef L, So EL, Ryvlin P, Tomson T (2012): Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 53, 227–233

Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR (2011): Incidence of epilepsy: A systematic review and meta-analysis. Neurology 77, 1005–1012

Niso G, Carrasco S, Gudín M, Maestú F, del-Pozo F, Pereda E (2015): What graph theory actually tells us about resting state interictal MEG epileptic activity. NeuroImage Clin 8, 503–515

Nolte G, Bai O, Wheaton L, Mari Z, Vorbach S, Hallett M (2004): Identifying true brain interaction from EEG data using the imaginary part of coherency. Clin Neurophysiol 115, 2292–2307

Olejniczak P (2006): Neurophysiologic Basis of EEG: J Clin Neurophysiol 23, 186–189

Olson IR, Plotzker A, Ezzyat Y (2007): The Enigmatic temporal pole: a review of findings on social and emotional processing. Brain 130, 1718–1731

Oostenveld R, Fries P, Maris E, Schoffelen JM (2011): FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Comput Intell Neurosci 2011, 1–9

Oto M (2017): The misdiagnosis of epilepsy: Appraising risks and managing uncertainty. Seizure 44, 143–146

Oyrer J, Maljevic S, Scheffer IE, Berkovic SF, Petrou S, Reid CA (2018): Ion Channels in Genetic Epilepsy: From Genes and Mechanisms to Disease-Targeted Therapies. Pharmacol Rev 70, 142–173

Panayiotopoulos CP (2005): Syndromes of Idiopathic Generalized Epilepsies Not Recognized by the International League Against Epilepsy. Epilepsia 46, 57–66

Patoner D (2021): Source analysis. http://wiki.cimec.unitn.it/tiki-index.php?page=Sourceanalysis2; accessed on 26.10.2021

Pegg EJ, Taylor JR, Mohanraj R (2020): Spectral power of interictal EEG in the diagnosis and prognosis of idiopathic generalized epilepsies. Epilepsy Behav 112, e107427

Peljto AL, Barker-Cummings C, Vasoli VM, Leibson CL, Hauser WA, Buchhalter JR, Ottman R (2014): Familial risk of epilepsy: a population-based study. Brain 137, 795–805

Pellegrino G, Mecarelli O, Pulitano P, Tombini M, Ricci L, Lanzone J, Brienza M, Davassi C, Di Lazzaro V, Assenza G (2018): Eslicarbazepine Acetate Modulates EEG Activity and Connectivity in Focal Epilepsy. Front Neurol 9, e01054

Penny WD, Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE: Statistical Parametric Mapping: The Analysis of Functional Brain Images. Elsevier, Amsterdam 2011

Petkar S, Hamid T, Iddon P, Clifford A, Rice N, Claire R, McKee D, Curtis N, Cooper PN, Fitzpatrick AP (2012): Prolonged implantable electrocardiographic monitoring indicates a high rate of misdiagnosis of epilepsy--REVISE study. Europace 14, 1653–1660

Pitsch J, Schoch S, Gueler N, Flor PJ, van der Putten H, Becker AJ (2007): Functional role of mGluR1 and mGluR4 in pilocarpine-induced temporal lobe epilepsy. Neurobiol Dis 26, 623–633

Placidi F, Marciani MG, Diomedi M, Scalise A, Giacomini P, Gigli GL (2000): Effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions in focal epilepsy: Sleep after LTG in epilepsy. Acta Neurol Scand 102, 81–86

Porteus SD: The Porteus Maze Test and Intelligence. Pacific Books, New York 1956

Quintas R, Raggi A, Giovannetti AM, Pagani M, Sabariego C, Cieza A, Leonardi M (2012): Psychosocial difficulties in people with epilepsy: A systematic review of literature from 2005 until 2010. Epilepsy Behav 25, 60–67

Quon RJ, Mazanec MT, Schmidt SS, Andrew AS, Roth RM, MacKenzie TA, Sajatovic M, Spruill T, Jobst BC (2020): Antiepileptic drug effects on subjective and objective cognition. Epilepsy Behav 104, e106906

Ratcliffe C, Wandschneider B, Baxendale S, Thompson P, Koepp MJ, Caciagli L (2020): Cognitive Function in Genetic Generalized Epilepsies: Insights From Neuropsychology and Neuroimaging. Front Neurol 11, e00144

Reitan RM: Trail Making Test. Reitan Neuropsychology Laboratory, Tucson, AZ 1992

Ribak CE, Hunt CA, Bakay RAE, Oertel WH (1986): A decrease in the number of GABAergic somata is associated with the preferential loss of GABAergic terminals at epileptic foci. Brain Res 363, 78–90

Ricci L, Assenza G, Pulitano P, Simonelli V, Vollero L, Lanzone J, Mecarelli O, Di Lazzaro V, Tombini M (2021): Measuring the effects of first antiepileptic medication in Temporal Lobe Epilepsy: Predictive value of quantitative-EEG analysis. Clin Neurophysiol 132, 25–35

Saad ZS, Reynolds RC (2012): SUMA. NeuroImage 62, 768–773

Sadleir LG, Scheffer IE, Smith S, Carstensen B, Farrell K, Connolly MB (2009): EEG features of absence seizures in idiopathic generalized epilepsy: Impact of syndrome, age, and state. Epilepsia 50, 1572–1578

Scheepers B, Clough P, Pickles C (1998): The misdiagnosis of epilepsy: findings of a population study. Seizure 7, 403–406

Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshe SL, et al. (2017): ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 58, 512–521

Schmidth M: Rey auditory verbal learning test: A handbook. Western Psychological Services, Los Angeles, CA 1996

Schneeweis N, Skirbekk V, Winter-Ebmer R (2014): Does Education Improve Cognitive Performance Four Decades After School Completion? Demography 51, 619–643

Schoffelen J-M, Gross J (2009): Source connectivity analysis with MEG and EEG. Hum Brain Mapp 30, 1857–1865

Schwindt P (2014): A Cryogen-Free, Low-Cost Atomic Magnetometer Array for Magnetoencephalography. https://grantome.com/grant/NIH/R01-EB013302-03; accessed on 06.09.2021

Seneviratne U, Cook M, D'Souza W (2014): Focal abnormalities in idiopathic generalized epilepsy: A critical review of the literature. Epilepsia 55, 1157–1169

Seneviratne U, Cook M, D'Souza W (2016): Consistent topography and amplitude symmetry are more typical than morphology of epileptiform discharges in genetic generalized epilepsy. Clin Neurophysiol 127, 1138–1146

Seneviratne U, Hepworth G, Cook M, D'Souza W (2017a): Can EEG Differentiate Among Syndromes in Genetic Generalized Epilepsy?: J Clin Neurophysiol 34, 213–221

Seneviratne U, Cook MJ, D'Souza WJ (2017b): Electroencephalography in the Diagnosis of Genetic Generalized Epilepsy Syndromes. Front Neurol 8, e00499

Shallice T (1982): Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci 298, 199–209

Shorvon S: Status Epilepticus: Its Clinical Features and Treatment in Children and Adults. Cambridge University Press, Cambridge 2006

Silva B, Canas-Simião H, Cordeiro S, Velosa A, Oliveira-Maia AJ, Barahona-Corrêa JB (2019): Determinants of quality of life in patients with drug-resistant focal epilepsy. Epilepsy Behav 100, e106525

Smith S, Nichols T (2009): Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. NeuroImage 44, 83–98

Smithson WH, Walker MC: ABC of Epilepsy. John Wiley & Sons, Hoboken, New Jersey 2012

Stam CJ, van Straaten ECW (2012): The organization of physiological brain networks. Clin Neurophysiol 123, 1067–1087

Stefan H, Paulini-Ruf A, Hopfengärtner R, Rampp S (2009): Network characteristics of idiopathic generalized epilepsies in combined MEG/EEG. Epilepsy Res 85, 187–198

Stier C, Elshahabi A, Hegner YL, Kotikalapudi R, Marquetand J, Braun C, Lerche H, Focke NK (2021): Magnetoencephalography reveals heritable brain networks in genetic generalized epilepsy. Neurology 97, 166–177

Sullivan JE, Dlugos DJ (2004): Idiopathic generalized epilepsy. Curr Treat Options Neurol 6, 231–242

Tangwiriyasakul C, Perani S, Centeno M, Yaakub SN, Abela E, Carmichael DW, Richardson MP (2018): Dynamic brain network states in human generalized spike-wave discharges. Brain 141, 2981–2994

The International League Against Epilepsy Consortium on Complex Epilepsies (2018): Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies. Nat Commun 9, e07524

Tomson T, Nashef L, Ryvlin P (2008): Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurol 7, 1021–1031

Tondelli M, Vaudano AE, Ruggieri A, Meletti S (2016): Cortical and subcortical brain alterations in Juvenile Absence Epilepsy. NeuroImage Clin 12, 306–311

Töne-Otto AI: Wechsler Gedächtnistest-Revidierte Fassung (WMS-R). In: Schellig D, Drechsler R, Heinemann D, Sturm W (Eds.). Hogrefe, Göttingen 2009, 749–760

Tousignant B, Sirois K, Achim AM, Massicotte E, Jackson PL (2017): A comprehensive assessment of social cognition from adolescence to adulthood. Cogn Dev 43, 214–223

Treiman DM (2001): GABAergic Mechanisms in Epilepsy. Epilepsia 42, 8–12

Vecchio F, Miraglia F, Quaranta D, Granata G, Romanello R, Marra C, Bramanti P, Rossini PM (2016): Cortical connectivity and memory performance in cognitive decline: A study via graph theory from EEG data. Neuroscience 316, 143–150

Vezzani A, Fujinami RS, White HS, Preux PM, Blümcke I, Sander JW, Löscher W (2016): Infections, inflammation and epilepsy. Acta Neuropathol (Berl) 131, 211–234

Vollmar C, O'Muircheartaigh J, Barker GJ, Symms MR, Thompson P, Kumari V, Duncan JS, Janz D, Richardson MP, Koepp MJ (2011): Motor system hyperconnectivity in juvenile myoclonic epilepsy: a cognitive functional magnetic resonance imaging study. Brain 134, 1710–1719

Wallace RH, Wang DW, Singh R, Scheffer IE, George AL, Phillips HA, Saar K, Reis A, Johnson EW, Sutherland GR, et al. (1998): Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel β1 subunit gene SCN1B. Nat Genet 19, 366–370

Wallace RH, Marini C, Petrou S, Harkin LA, Bowser DN, Panchal RG, Williams DA, Sutherland GR, Mulley JC, Scheffer IE, Berkovic SF (2001a): Mutant GABAA receptor γ2-subunit in childhood absence epilepsy and febrile seizures. Nat Genet 28, 49–52

Wallace RH, Scheffer IE, Barnett S, Richards M, Dibbens L, Desai RR, Lerman-Sagie T, Lev D, Mazarib A, Brand N, et al. (2001b): Neuronal Sodium-Channel a1-Subunit Mutations in Generalized Epilepsy with Febrile Seizures Plus. Am J Hum Genet 68, 859–865

Wandschneider B, Kopp UA, Kliegel M, Stephani U, Kurlemann G, Janz D, Schmitz B (2010): Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. Neurology 75, 2161–2167

Wei H, An J, Shen H, Zeng LL, Qiu S, Hu D (2016): Altered Effective Connectivity among Core Neurocognitive Networks in Idiopathic Generalized Epilepsy: An fMRI Evidence. Front Hum Neurosci 10, e00447

Weidlich S, Hartje W, Derouiche A, Hillers F: DCS-II: Diagnosticum für Cerebralschädigung-II: ein figuraler visueller Lern-und Gedächtnistest nach F. Hillers. Huber, Mannheim 2011

Weir B (1965): The Morphology of the Spike-Wave Complex. Electroencephalogr Clin Neurophysiol 19, 284–290

Whittingstall K, Stroink G, Gates L, Connolly J, Finley A (2003): Effects of dipole position, orientation and noise on the accuracy of EEG source localization. Biomed Eng OnLine 2, e925214

Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE (2014): Permutation inference for the general linear model. NeuroImage 92, 381–397

Winter WR, Nunez PL, Ding J, Srinivasan R (2007): Comparison of the effect of volume conduction on EEG coherence with the effect of field spread on MEG coherence. Stat Med 26, 3946–3957

World Medical Association (2008): Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Jahr Wiss Ethik 14, 233–237

Ystad M, Hodneland E, Adolfsdottir S, Haász J, Lundervold AJ, Eichele T, Lundervold A (2011): Cortico-striatal connectivity and cognition in normal aging: A combined DTI and resting state fMRI study. NeuroImage 55, 24–31

Yu FH, Mantegazza M, Westenbroek RE, Robbins CA, Kalume F, Burton KA, Spain WJ, McKnight GS, Scheuer T, Catterall WA (2006): Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nat Neurosci 9, 1142–1149

Zarrei M, MacDonald JR, Merico D, Scherer SW (2015): A copy number variation map of the human genome. Nat Rev Genet 16, 172–183

Zhou L, Ma X, Wang W (2021): Relationship between Cognitive Performance and Depressive Symptoms in Chinese Older Adults: The China Health and Retirement Longitudinal Study (CHARLS). J Affect Disord 281, 454–458

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Lebenslauf

Ich wurde am 11.07.1990 in Kiel geboren.

Von 1997 - 2001 besuchte ich die Grundschule Suchsdorf und im Anschluss das Ernst-Barlach-Gymnasium, wo ich im Juni 2010 mein Abitur abschloss.

Als Wehrdienstverweigerer absolvierte ich von 2010 - 2011 ein freiwilliges soziales Jahr in der Kindertagesstätte des deutschen roten Kreuzes in Suchsdorf, Kiel.

2011 begann ich mein Psychologie-Studium an der der Universität Ulm, welches ich 2014 zunächst mit dem Bachelor-of-Science und 2016 dann mit dem Master-of-Science abschloss.

Nach 6-monatiger Tätigkeit als wissenschaftlicher Mitarbeiter in der neuropsychologischen Abteilung des Rehabilitationsklinikums Ulm unter Leitung von PD Dr. Dorothée Lulé begann ich mein Medizinstudium im April 2017 an der Georg-August-Universität in Göttingen. Während des klinischen Abschnitts fing ich dann im Dezember 2019 mit meiner Doktorandentätigkeit in der Klinik für Neurologie an der Universitätsmedizin Göttingen an.

Das Medizinstudium werde ich voraussichtlich nach 12 Semestern im Sommer 2023 abschließen.