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**Brainmapping  
Neuronal Networks in Children with Continuous Spikes and  
Waves during Slow Sleep as revealed by DICS and RPDC**

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# 1 INTRODUCTION

## 1.1 CSWS-SYNDROME

Epileptic encephalopathy with CSWS (continuous spike and wave during slow sleep) is an age-related, partly reversible syndrome and is characterized by the triad of seizures, psychomotor deficits and the detection of a continuous spike-and-wave-pattern during non-REM sleep in the EEG (Panayiotopoulos, 2005). The definition of this pattern demands that it appears in at least 85% of the non-REM sleep (Tassinari et al., 2000) (Siniatchkin et al., 2010) and can be recorded at least three times over a time period of at least one month (Tassinari et al., 2000). The cut-off value of 85% has been defined by Patry et al. 1971, but as there are no quantitative studies on CSWS-percentage during sleep (Khan and Al Baradie, 2012), other authors demand a significant activation of the pattern during slow sleep for the diagnosis (Tassinari et al., 2009, Van Hirtum-Das et al., 2006).

CSWS is both considered a discrete syndrome in the ILAE-report of 2010 but also an electroencephalographic pattern, which appears in the context of patients diagnosed for example with ABPE (atypical benign partial epilepsy)/ Pseudo-Lennox-Syndrome (Panayiotopoulos, 2005), acquired opercular syndrome (Brazzo et al., 2012) or LKS (Landau-Kleffner-Syndrome) (Hughes, 2011). This is one of the reasons why the diagnostic borders between all those syndromes belonging to the epileptic encephalopathies in infancy and early childhood (Panayiotopoulos, 2005) are vague and are even considered overlapping (Hahn et al., 2001). Next to "CSWS" there is another term, used in the literature, which is ESES (electrical status epilepticus during sleep). Depending on the author read, one or the other can be found, as they are used mainly synonymously (Hughes, 2011).

### 1.1.1 Historical Background

The first time a "subclinical electrical status epilepticus induced by sleep in children" was described goes back to Patry et al in 1971 (Patry et al., 1971). He points out the differences compared to the earlier described Landau-Kleffner-Syndrome (Landau and Kleffner, 1957) but doesn't create the association to clinical symptoms, yet. The linkage to the development of an encephalopathy was published by Tassinari et al in 1977, renaming this electroencephalographic pattern SES (status epilepticus during slow sleep) (Tassinari et al., 1977). The ILAE-report of 1989 refers to this complex of characteristics as the more descriptive term of CSWS. The diagnostic triad mentioned earlier was then developed throughout the following years.

### 1.1.2 Demographic data

The incidence of the CSWS-Syndrome is low and a definite value can still not be named (Tassinari et al., 2000), not least due to the fact that the classification of epileptic encephalopathies during childhood is overlapping and still in progress. There are only assumptions found in literature of about 0,2-0,5% of all epilepsies during childhood (Veggiotti et al., 2012).

The onset lies between 2 months and 12 years (Panayiotopoulos, 2005), with a peak from 4 to 5 years (Tassinari et al., 2000).

Regarding the sex distribution there seems to be a slight tendency in favor of the male patients by 62 % (Panayiotopoulos, 2005).

### 1.1.3 Etiology and Pathogenesis

The etiology and pathophysiology of CSWS is still not completely understood (Brazzo et al., 2012).

Regarding the etiology most of the cases are cryptogenic. Recent studies name chromosomal structural aberrations like 8p-deletion, 9p-duplication, dup X (p11.22-p11.23) (Brazzo et al., 2012) or deletion of 16p13 including GRIN2A, coding for a subunit of the NMDA-receptor (Reutlinger et al., 2010). All of them are mentioned in the context of supporting the development of CSWS. But Tassinari still points out that the genetic factors play a minor role for the etiology (Tassinari et al., 2000).

Also brain lesions may contribute to the development of this encephalopathy, especially polymicrogyria, porencephaly, thalamic lesions, migrational disorders and a shunted hydrocephalus (Brazzo et al., 2012).

Therefore two types of CSWS are possible: symptomatic and idiopathic (Hughes, 2011).

During brain maturation epileptic activity is a main cause for progressive cognitive and neuropsychological regression. In what way the brain reacts to epileptic predisposition, combined with the elevated neocortical excitability of an immature brain, depends on the stage of brain maturation and, therefore, the resulting migrational disorder. This explains the different EEG patterns observed for the different entities of age-related encephalopathies (Khan and Al Baradie, 2012).

Beenhakker and Huguenard explained in 2009 that normal brain circuits are used as templates for epileptic circuits to generate seizures (Beenhakker and Huguenard, 2009). During non-REM sleep the afferences to the thalamical relais neurons, which are active during wakefulness, are reduced to a minimum. This leaves the relais-neurons in a rhythmic, synchronized oscillating mode, projecting towards neocortical neurons which can be seen as delta-waves in EEG-recordings (Klinke, 2009). For absence seizures it is known that 3-Hz-

spike-and-wave-patterns are derived by a combination of elevated excitability and increased synchronization of the oscillatory activity of the thalamocortical system (Klinke, 2009).

All this information combined might explain why the characteristic generalized spike-and-wave-pattern observed for CSWS appears during non-REM sleep in the immature brain.

To approach the understanding of the pathogenesis two main questions need to be answered: (1) how is the ESES generated and (2) what is the reason for the psychomotor impairments (Tassinari et al., 2000).

The first question is partly answered above. In addition it is assumed that the ESES is based on a secondary bilateral synchrony. Evidence includes EEG-based interhemispheric peak latencies, focal EEG-activity during wakefulness and REM-sleep and partial motor seizures, which are the main seizure type (Tassinari et al., 2000).

Regarding the second issue, a distinction between the pathophysiology of the pattern and the severity of impairments seems useful. There is a strong association between the individual localization of paroxysmal activity and the pattern of clinical deterioration of each patient (Tassinari et al., 2000). Also Van Bogaert points out clinical, neurophysiological and metabolic linkage between IED (interictal epileptiform discharges) and “cognitive deficits by interfering with the neuronal networks at the site of the epileptic foci but also at distant connected areas” (Van Bogaert, 2013). Concerning the severeness of deterioration the effect of ESES itself cannot be ignored. Clinical performance of all patients decreases tremendously with the onset of ESES irrespective of a normal or abnormal development before onset (Tassinari et al., 2000). On the contrary an improvement is observed during puberty, when the ESES stops (Singhal and Sullivan, 2014). Singhal and Sullivan also emphasize the relevance of the spike-wave-index, which is defined as *minutes of spike-and-wave-abnormalities divided by total minutes of non-REM-sleep multiplied by 100* (Brazzo et al., 2012), as an increase also means an increase in neuropsychological impairment (Singhal and Sullivan, 2014).

Another hypothesis refers to the disturbance of neuroplasticity processes during sleep which are indispensable for learning and memory consolidation (Tassinari et al., 2009). This also leads back to the deteriorated thalamo-cortical system, which normally derives sleep spindles during non-REM-sleep. In a normal-functioning brain sleep spindles appear more often after intensive learning periods, can induce synaptic changes and are associated with hippocampal activity. Therefore they are believed to contribute to memory consolidation and

neuroplasticity processes, which are missing in the case of a pathological thalamo-cortical system. (Beenhakker and Huguenard, 2009)

#### **1.1.4 Clinical Manifestation**

Clinical manifestation of CSWS is a combination of neuropsychological and motor impairment on the one hand and the appearance of various seizure types on the other. (Khan and Al Baradie, 2012)

Seizures can be the first sign, 1-2 years before the onset of CSWS, or there can be signs of abnormal development beforehand (Khan and Al Baradie, 2012).

In less than 20% of all cases neurocognitive regression can be observed without the presence of clinical seizures (Singhal and Sullivan, 2014).

##### Neuropsychological and motor deterioration

The neuropsychological deterioration can be selective or global (Tassinari et al., 2000). It hardly ever excludes verbal abilities and achievements concerning attention (Khan and Al Baradie, 2012). Other impairments, often observed, affect temporospatial skills, short-term memory combined with hyperactivity and aggression (Brazzo et al., 2012).

Roulet Perez et al. compare the patterns found even to developmental autistic-like disorders (Roulet Perez et al., 1993).

Dystonia, dyspraxia, ataxia (Brazzo et al., 2012), unilateral deficits and negative myoclonus (Tassinari et al., 2000) are examples for motor deficits.

Which combination of impairments can be observed in each patient varies interindividually and seems to depend on the localization of the interictal foci (Tassinari et al., 2009).

Panayiotopoulos describes two main types: The ones with the (pre-)frontal foci with enhancement of “hyperkinesia, agitation, disinhibition, aggressiveness and inattention” and, on the other hand, the ones with the temporal foci and therefore linguistic disturbances with a tendency towards expressive aphasia (Panayiotopoulos, 2005).

The development is subacutely progressive and shows spontaneous fluctuations. In addition, an improvement can be induced by discharge-suppression (Tassinari et al., 2009). With the end of CSWS, a reversibility of the regression is possible (Roulet Perez et al., 1993).

##### Seizure types

Regarding the seizures which appear in the context of CSWS, nearly all types can be observed except for tonic seizures (Khan and Al Baradie, 2012). Examples are uni- and



bilateral clonic seizures, GTCS (generalized tonic-clonic seizures), epileptic falls, absences, partial motor seizures and complex partial seizures. Before the onset of CSWS, 80% of all cases show only one specific seizure type (Singhal and Sullivan, 2014). But with the occurrence of the CSWS there can be seen more than one type in around 60 % and in addition an increase in severeness and frequency (Khan and Al Baradie, 2012). Nevertheless less than 70% of all patients suffer from more than one seizure per day (Singhal and Sullivan, 2014).

Tassinari et al point out that there is a difference in incidence depending on whether the seizure occurs out of sleep or during wakefulness. During sleep, partial motor seizures and unilateral seizures can be observed most commonly. During wakefulness, absences and epileptic falls are more frequent (Tassinari et al., 2000).

### **1.1.5 EEG-Findings**

To describe the EEG-findings for this encephalopathy the division into three stages is necessary.

Before the onset of CSWS the background activity can either be normal or abnormal. The abnormalities consist of focal sharp-waves or slow-spikes in the fronto- or centrotemporal region. In 80% of all cases a diffuse appearance is also possible. They can always be detected but are already emphasized during sleep (Singhal and Sullivan, 2014) (Panayiotopoulos, 2005). There is no alteration in sleep-cycling and the presence of typical EEG-patterns in the different sleep stages (Panayiotopoulos, 2005).

In the second stage, with the onset of CSWS, the background activity, which can be observed during wakefulness and REM-sleep, resembles a more marked form of the one, recorded before the onset of CSWS.

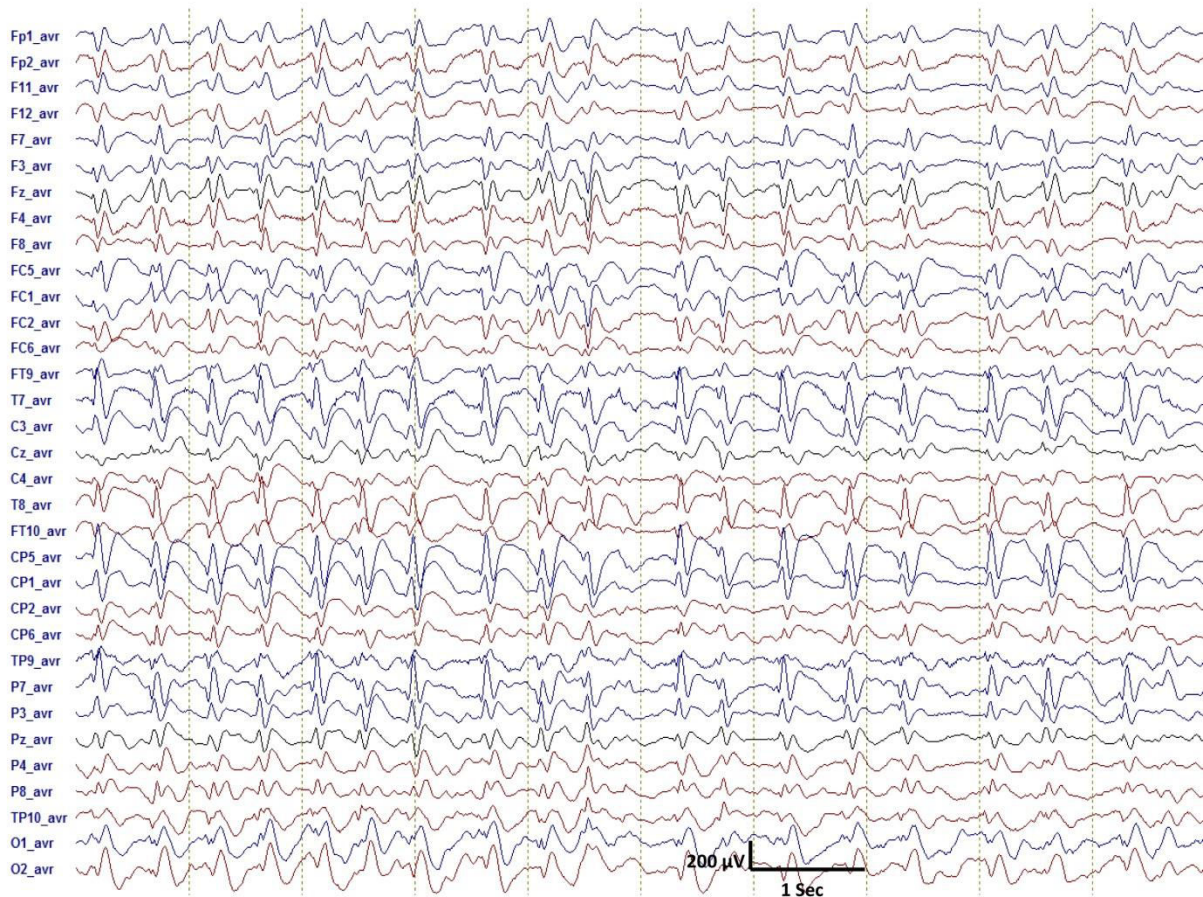
The description of the EEG during non-REM sleep leads back to the hallmark of CSWS: Although there are no quantitative studies on CSWS percentage during non-REM sleep (Khan and Al Baradie, 2012), most authors consider > 85% as basis for the diagnosis of this syndrome (Tassinari et al., 2000, Siniatchkin et al., 2010). Bilateral, diffuse spike-waves of a 1,5-2 Hz-frequency are present, which have a focal onset and generalize secondarily. Also slow spikes without waves (Tassinari et al., 2000) and faster rates of 3-4 Hz are possible (Tassinari et al., 2000) (Panayiotopoulos, 2005). The focal onsets correspond to the interictal foci during wakefulness and are still emphasized, even during the electrical status during sleep. (Panayiotopoulos, 2005)

The sleep cycling is not altered, but the characteristic patterns like sleep-spindles, vertex spikes and K-complexes only appear in cases where the ESES is fragmented (Panayiotopoulos, 2005).

Parallel to the focal onset and secondarily generalization during the subclinical status during sleep, the clinically apparent seizures also all have a focal onset. This can be proven by observing interhemispheric peak latencies in ictal EEG-recordings (Khan and Al Baradie, 2012).

An example of a sleep-EEG recorded during the second stage of CSWS can be seen in figure 1.

With the end of the CSWS the third stage is reached. The discharges during non-REM sleep become more fragmented, shorter and less frequent. The background activity, with focal sharp-/ slow-waves may persist for several more years (Panayiotopoulos, 2005).



**Figure 1: an example of a sleep-EEG recorded during the second stage of CSWS showing generalized spike and wave discharges and slow spikes**

### 1.1.6 Neuroimaging

Regarding the techniques of neuroimaging concerning the CSWS-syndrome, FDG-PET (fluorodeoxyglucose - positron emission tomography) and fMRI (functional MRI) have played the most prominent role. The technique of FDG-PET is based on displaying regional perfusional changes (neurovascular coupling to neuronal activity), the technique of fMRI on differences in regional glucose consumption (neurometabolic coupling of neuronal activity). (De Tiege et al., 2009)

In 2010 Siniatchkin et al studied 12 patients suffering from CSWS, including cryptogenic and symptomatic cases, by simultaneous recording of EEG and fMRI. Siniatchkin postulates that areas of spike-related BOLD (blood oxygen level dependent) - activation correspond either to initiation or propagation pathways of the epileptic activity. The cingulate cortex and the bilateral perisylvian region are involved in all cases, the thalamus and the bilateral frontal region in 5 and the bilateral parietal cortex in one case. Interindividually the site of origin of the epileptic activity differs, but all 12 patients show a propagation towards the bilateral perisylvian region. This pattern is claimed specific for CSWS by Siniatchkin et al. Simultaneously, a spike-related BOLD-deactivation can be observed in areas of the default mode network, which includes the precuneus, the parietal cortex and the frontal cortex and, in 4 cases, also the caudate nucleus. (Siniatchkin et al., 2010)

This deactivation is found in several studies and is explained by a remote inhibition of distant connected areas (Siniatchkin et al., 2010, De Tiege et al., 2009). It corresponds to findings of regional hypometabolism in FDG-PET-studies (Ligot et al., 2014, De Tiege et al., 2009, De Tiege et al., 2008).

Ligot et al included only cryptogenic cases of CSWS using FDG-PET, and again the bilateral perisylvian region can be proven as a hypermetabolic area. The hypometabolic areas are described as key nodes of the default mode network (mesial and lateral prefrontal gyrus, precuneus, posterior cingulate cortex and parahippocampal gyri). In addition, Ligot et al found an altered connectivity between the hypo- and hypermetabolic sites, compared to a control-group of patients with focal cryptogenic activity without CSWS. (Ligot et al., 2014)

De Tiège et al examined the metabolic changes of 9 CSWS-patients and found a hypermetabolism in the centroparietal regions and the right fusiform cortex. The hypometabolism was located in the pre-/orbitofrontal cortices, the temporal lobes, the left parietal cortex, the precuneus and the cerebellum. They compared the results of the active phase with the recovery phase and observed a regression of those metabolic alterations. (De Tiege et al., 2008)

All in all the prominent areas of hypermetabolism, respectively BOLD-activation, are all located cortical, so that Ligot et al claim a primary involvement of the cortex in the CSWS-genesis. (Ligot et al., 2014) These are the sites considered as the origin for the epileptic

activity (De Tiege et al., 2013, De Tiege et al., 2009, Siniatchkin et al., 2010), whereas the hypometabolic, respectively BOLD-deactivated, areas seem to be inhibited consecutively, which contributes to the psychomotor regression. (Ligot et al., 2014, De Tiege et al., 2009)

### **1.1.7 Development and Prognosis**

The development of the CSWS-Syndrome can be divided into different phases. There is the acute phase, characterized by the CSWS-pattern in the EEG, the emergence and progression of psychomotor deficits and seizure activity (De Tiege et al., 2008). This period can last from several months up to 6-7 years (Panayiotopoulos, 2005) and is followed by a recovery phase with a partly remission of clinical impairments and the disappearance of the distinct EEG-pattern (Panayiotopoulos, 2005, De Tiege et al., 2008). In addition to that Panayiotopoulos also describes a third stage, 1-2 years prior to the active one: The EEG doesn't reveal the typical anomalies yet, but first infrequent seizures can be observed (Panayiotopoulos, 2005, Khan and Al Baradie, 2012).

The prognosis concerning the EEG-characteristics and the seizures is good. Both disappear after the completion of the third phase around the age of 10-15 years (Panayiotopoulos, 2005) and are therefore self-limited, independent of the cause of the encephalopathy (Khan and Al Baradie, 2012). In some cases focal interictal spikes can persist (Khan and Al Baradie, 2012).

With the interruption of seizures and CSWS, an improvement, or at least a stabilization, of the clinical impairments can be observed. The process of improvement is rather slow and in most cases incomplete, especially regarding attention and verbal abilities (Panayiotopoulos, 2005). The final clinical outcome depends on various parameters: Seizure frequency and duration of CSWS are considered the most important (Singhal and Sullivan, 2014), but early age of onset and an abnormal development prior to the onset also contribute to a less favorable prognosis. (Panayiotopoulos, 2005)

All in all Panayiotopoulos regards less than 25% of all patients as capable of reaching a, what he calls "acceptable social and professional level" (Panayiotopoulos, 2005).

### **1.1.8 Treatment**

The main aim of therapy correlates with the most important influencing factors of the clinical outcome: reducing seizure frequency and ESES-duration (Singhal and Sullivan, 2014). As the pattern of neuropsychological impairment and interictal epileptic activity are clearly

associated with each other, some authors also include the suppression of the IED as a therapy target (Tassinari et al., 2000).

AEDs (antiepileptic drugs) play a big role, although general treatment guidelines (dose, when to start and for how long, continuous or pulsatile usage) are still lacking (Pera et al., 2013) and epileptic encephalopathies are generally considered refractory to AEDs (Khan and Al Baradie, 2012).

Opinions, which drugs are useful and which ones can even worsen the symptoms, are also vague. A lot of studies can be found with different results and often small populations (Veggiotti et al., 2012). In addition many positive effects on the EEG, the impairments or the seizure frequency are only transient. (Khan and Al Baradie, 2012)

Nevertheless, Valproat, Ethosuximid, Benzodiazepines (Singhal and Sullivan, 2014) and Levetiracetam for cases with structural brain lesions (Veggiotti et al., 2012) are considered the first line therapy. Carbamazepine, Phenytoin and Phenobarbital should be avoided (Khan and Al Baradie, 2012, Veggiotti et al., 2012, Panayiotopoulos, 2005).

In more severe cases, when AEDs are not effective enough, steroids and ACTH can be applied, both chronical or pulsatile (Veggiotti et al., 2012). Figure 2 shows an exemplary approach for the drug treatment.

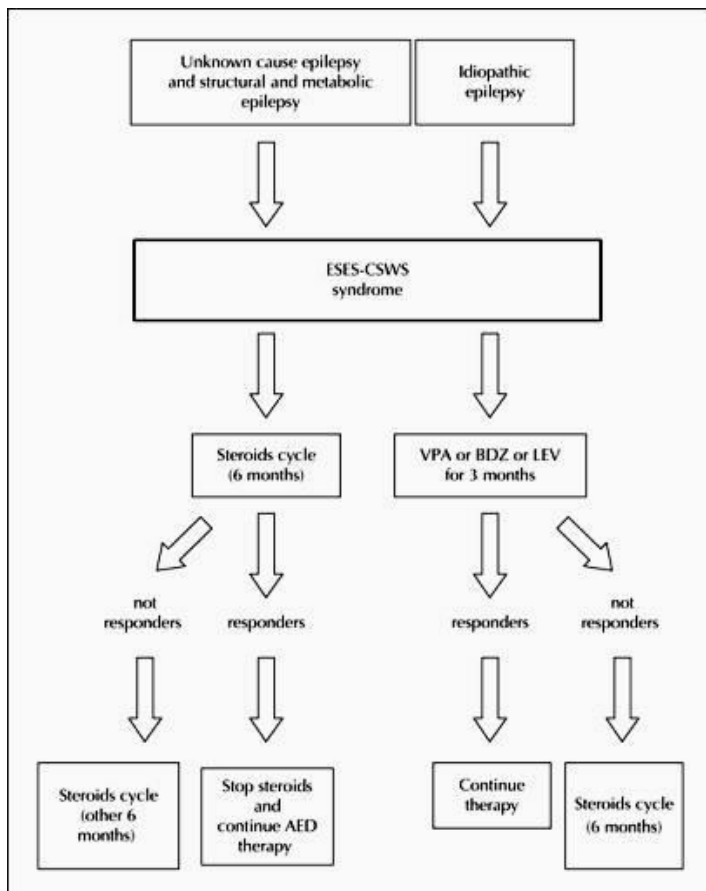


Figure 2: Flowchart of an approach for drug treatment (Veggiotti et al., 2012) (VPA: valproat, BDZ: benzodiazepine, LEV: levetiracetam)

Positive effects have also been shown for vagus nerve stimulation (Pera et al., 2013), in cases of LKS also for a ketogenic diet (Singhal and Sullivan, 2014) and occasionally surgical options like subpial intracortical transection (Veggiotti et al., 2012) and hemispherectomy (Hughes, 2011).

To complete the management of this syndrome, it should always be accompanied by speech and occupational just as physiotherapy.

### **1.1.9 Characteristics Landau-Kleffner-Syndrome**

Around 0,2% of the epileptic population suffers from LKS (Brazzo et al., 2012) and the sex-distribution is estimated as 1,7:1 in favor of the male (Khan and Al Baradie, 2012).

Comparing onset-age, seizure-types, EEG-features, metabolic dysfunctions in PET-studies, long-term-prognosis and therapeutic approach LKS is identical to CSWS itself. This is the reason for the LKS being classified as a special form of appearance of the CSWS (Tassinari et al., 2000). Hughes, on the other hand, points out that children suffering from LKS show less global regression and a lower seizure frequency. In addition symptomatic cases with proof of brain lesions are rare (Hughes, 2011).

The hallmark of LKS, next to the clinical symptoms described for CSWS, is the acquired aphasia, which coincides with the appearance of ESES in mostly healthy children. The subacute and progressive development starts with an auditory agnosia and is followed by an expressive language impairment (Brazzo et al., 2012, Singhal and Sullivan, 2014).

Also for LKS interictal discharges, mostly frontal or temporal spikes, are detected in EEG-recordings. Around 67% of all patients show a left temporal focus, and bitemporal discharges go along with an aggravation of the acquired aphasia (Hughes, 2011). In an MEG (magnetoencephalography) - study, the spike generator was located in the perisylvian cortex (68%), mostly bilateral (Sobel et al., 2000, Paetau, 2009).

### **1.1.10 Characteristics ABPE/ Pseudo-Lennox-Syndrome**

Atypical Benign Partial Epilepsy is not accepted as a distinct syndrome by the ILAE but is rather considered a more severe form of the Rolandic epilepsy (Fujii et al., 2010). The Rolandic epilepsy may include mild cognitive and behavioural difficulties, but patients with ABPE show an earlier onset (2,5-6 years), more frequent spikes-/ spike-and-wave-discharges, more severe neuropsychological impairments and CSWS (Fujii et al., 2010, Fejerman, 2009).

Comparing the sex distribution, girls are slightly more often affected, but their average onset-age is higher and the development of the syndrome less defacing (Hahn et al., 2001).

The etiology is multifactorial, but the genetic influence seems to play a major role. Although the mode of inheritance is unclear, a hereditary impairment of brain maturation seems likely (Doose et al., 2001).

As described for CSWS-syndrome itself, focal abnormalities in the EEG generalize during sleep also in patients, which suffer from ABPE. Fejerman et al located these foci most often in the centrotemporal region using EEG (Fejerman et al., 2000), whereas Shiraishi found them in the Rolandic-Sylvian-region using MEG (Shiraishi et al., 2014).

Again, various seizure types, mostly secondarily generalized, are compatible with the diagnosis of ABPE, but no tonic seizures are observed (Hahn et al., 2001). Negative epileptic myoclonus is a very typical seizure type, but drop attacks, focal motor seizures are more frequent and atypical absences can also appear (Shiraishi et al., 2014).

The focal onsets include orofacial areas or unilateral limbs (Fujii et al., 2010).

The term “Pseudo-Lennox-Syndrome” as a synonym was introduced by Doose, 1989, who discovered semiologic parallels between the ABPE and the LGS (Lennox-Gastaut-Syndrome) (Doose et al., 2001). But in contrast to the ABPE, seizures do not fade with puberty, tonic seizures may appear and fast spike series just as bursts of 10-20Hz rhythms can be observed in case of LGS (Hahn et al., 2001).

## 1.2 SOURCE ANALYSIS

“Localizing the different modules of the functional network implicated in a given mental task is the principal aim of functional neuroimaging” (Michel et al., 2004). This is how Michel et al. describe the meaning of source analysis. Next to the application in epileptic research it is also implemented in other departments of neuroscience like psychiatry or psychopharmacology (Michel et al., 2004).

Comparing the methods used for source imaging, a main difference can be found in the temporal and spatial resolution. There is the FDG-PET, the ictal SPECT (single photon emission computer tomography) and the fMRI on the one hand with a high spatial but a low temporal resolution and a very limited time frame for recording (Moeller et al., 2013, Michel et al., 2004, Elshoff et al., 2013). Therefore the localization of the involved regions in a neuronal network may be more exact but conclusions concerning the interrelationship between the individual sources remain unclear (Michel et al., 2004).

On the other hand there is the EEG and the MEG measuring changes in neuronal activity in a submillisecond time scale (Michel et al., 2004), so that for example sites of origin and propagation in an epileptic network can be differentiated (Siniatchkin et al., 2010). Both

methods, EEG and MEG, are recordings that are based on potentials measured on the scalp surface, without directly indicating the location of the active neurons. Especially deep brain structures are difficult to locate (Moeller et al., 2013). To find those sources the static electromagnetic inverse problem (Moeller et al., 2013), first described by Helmholtz 1853, needs to be solved (Michel et al., 2004). It gives answers to the question, where exactly the sources are located that are the origin of the specific pattern of potentials measured on the scalp (Gross et al., 2001).

DICS (dynamic imaging of coherent sources) is one of those inverse solutions and was implemented by Gross et al. in 2001 (Gross et al., 2001). It is a linearly constrained minimum variance beamforming method that uses a spatial filter in the frequency domain to compute a topographical map of the entire brain for power and coherence (Händel, 2010, Michel et al., 2004, Gross et al., 2005). The DICS-error is estimated at  $\leq 1,5$  mm and  $\leq 4^\circ$  for the source localization in cortical areas (Gross et al., 2001). An important requirement for this method is an MRI-based head model, for example a volume conduction model constructed by the boundary element method (Muthuraman et al., 2008). Some authors also call this the solution of the forward problem (Gross et al., 2001, Michel et al., 2004): It estimates the scalp potentials of each possible source, incorporating the different conductivity properties of different parts of the brain, the skull and the skin (Michel et al., 2004, Van Veen et al., 1997, Händel, 2010).

DICS can be applied to either MEG- or EEG-data (Gross et al., 2001). Examples for studies using EEG-data can be found by Japaridze et al and Moeller et al, who revealed epileptic networks for West Syndrome and absences, including deep brain structures like caudate nucleus, brainstem, putamen (Japaridze et al., 2013) and thalamus (Moeller et al., 2013).

Coherence, and therefore DICS, is able to reveal the sources participating in a neuronal network. But the direction of information flow remains unclear (Moeller et al., 2013). For this part of source analysis another method needs to be applied. RPDC (renormalized partial directed coherence) is one of those and was first described by Schelter in 2009 (Moeller et al., 2013). It is based on the principle of Granger causality (Schelter et al., 2009):

“Given two time series  $a(t)$  and  $b(t)$ ,  $a(t)$  is said to Granger-cause  $b(t)$  if the insertion of  $a(t)$ 's past into an autoregressive modelization of  $b(t)$  significantly improves prediction of  $b(n)$ , that is, if it reduces the prediction error. “(Astolfi)



### **1.3 AIM OF THE STUDY**

The aim of the study is to investigate the neuronal network which is active during the CSWS-discharges and how it changes after treatment. As there is the assumption that the epileptic activity is responsible for the psychophysiological impairment of the children (Van Bogaert, 2013), the interpretation of the network, especially the analysis of the connectivity, the direction of the information flow and its changes after treatment, may contribute to the better understanding of the pathogenesis of the clinical manifestations.

The source analysis results for the CSWS-Syndrome currently available in literature are based on fMRI (Siniatchkin et al., 2010) or on PET (De Tiege et al., 2013, De Tiege et al., 2008, Maquet et al., 1995, Ligot et al., 2014), two methods revealing a good partial resolution but lacking a good temporal one. Performing the source analysis based on the EEG with a temporal resolution in the order of milliseconds (Ray et al., 2007) will therefore include a method with the exact opposite characteristics to compare the different results.

## **2 MATERIAL AND METHODS**

The study was conducted according to the Declaration of Helsinki (current version, 2013) on biomedical research involving human subjects (Tokyo amendment). Parents or legal guardians of participants gave their informed consent for using the data in anonymous way for the research purposes.

### **2.1 SUBJECTS OF THE STUDY**

From the database of the Epilepsy Centre in Raisdorf and the Neuropaediatric Department of the University of Kiel 12 subjects, 6 male and 6 female, were chosen. All of them were diagnosed with an epileptic encephalopathy (11 patients with ABPE/ Pseudo-Lennox-Syndrome and one with CSWS), according to the ILAE 2001 classification scheme, in addition to fulfilling the diagnostic properties of a CSWS in the EEG. Another condition, applied to the selection of the patients, was the finding of a non-pathological MRI, accepting small variants within the norm.

The medical reports of all patients over a median of 41,5 months (3-73 months) were reviewed in order to collect information about family history, difficulties during pregnancy or birth, mental and physical disorders, seizure control, EEG-characteristics and drug treatment. On average the patients were 6 10/12 years old, when the electrical status during slow sleep was diagnosed the first time (in case the CSWS-onset was unclear, the date of the first EEG-recording showing the required characteristics was taken).

Demographic and clinical data are summarized in table 1, the individual impairments and specifications concerning development during early childhood and family history are listed in table 2 and data of the employed EEGs and MRIs can be found in table 3.

**Table 1: Demographic and clinical data of the study population. (AA – Atypical Absence, A – Absence, AS – Atonic Seizure, CPS – Complex Partial Seizure, EM – Eyelid Myoclonus, GTCS – Generalized Tonic Clonic Seizure, PS – Partial Seizure, PSS – Perisylvian Seizure, SGTC – Secondary Generalized Tonic Clonic Seizure, TAS – Tonic Astatic Seizure, CBZ – Carbamazepin, CLB – Clobazam, DXM – Dexamethason, ETX – Ethosuximid, LCM – Lacosamid, LEV – Levetiracetam, LTG – Lamotrigin, PB – Phenobarbital, PPN – Perampanel, STM – Sultiam, TPM – Topiramate, VPA – Valproate)**

Subject	Gender	DOB	Diagnosis	Age of Onset (years)	Seizure Types	Seizure Frequency (/month)	Drugs
1	M	10/1998	ABPE	5 10/12	CPS	0,2	ETX, VPA
2	M	02/1997	ABPE	9 11/12	EM	0,02	STM, VPA, LEV
3	M	09/2000	ABPE	8 7/12	SGTC, GTCS, CPS, A	0,5	STM, CLB, PPN, ETX, DXM
4	F	12/2001	ABPE	9 2/12	AA, GTCS	0,03	ETX, DXM, CBZ
5	M	07/1999	ABPE	4 3/12	AS	0	VPA, STM, LEV, DXM
6	F	05/2000	ABPE	7 8/12	EM, CPS	0,02	ETX, LEV, LTG, STM
7	F	03/1994	CSWS	6 4/12	AA, SGTC	0,03	VPA, DXM, LTG, ETX
8	F	06/2002	ABPE	5 8/12	A, AS, GTCS	300	LTG, LEV, CLB
9	M	07/1992	ABPE	8 2/12	PS, AA, TAS, GTCS	10	DXM, ETX, STM, PB, TPM, CLB
10	F	09/2004	ABPE	5 1/12	CPS, SGTC, PSS	0,06	DXM, ETX, LEV, VPA, LCM
11	M	06/2007	ABPE	3 3/12	AA, AS, CPS, EM	8	ETX, DXM
12	F	07/1998	ABPE	9 0/12	GTCS, AS	0	VPA

**Table 2: Individual impairments, specifications concerning development during early childhood and family history of the study population. (n.k. – not known, - - no anomaly documented, + - anomaly documented (family history: neurological disease including epilepsy, autism or ADHD in 1<sup>st</sup>-grade relatives))**

Subject	Development	Family History	Aggression/Frustration Tolerancy ↓	Fine Motor Skills ↓	Memory Deficit	Concentration-/Attention Deficit	Speech Disorder	Gross Motor Skills ↓	Tremor	Visual-Spatial Orientation ↓	Handling of Numbers	Number of Impairments
1	-	+	+	+	+	+	+	-	-	-	-	6
2	+	-	+	+	+	+	-	-	-	+	-	6
3	-	-	+	-	+	+	-	-	-	-	+	4
4	n.k.	+	-	+	+	+	-	+	+	+	-	7
5	+	+	+	+	+	-	+	+	-	-	-	7
6	-	+	-	-	+	+	-	-	-	+	+	5
7	-	-	+	+	-	+	-	-	-	-	-	4
8	+	+	+	+	-	-	-	-	-	+	+	6
9	n.k.	n.k.	+	+	+	+	+	+	+	-	+	8
10	+	n.k.	+	+	+	+	+	+	+	+	+	9
11	n.k.	n.k.	+	+	-	+	-	+	-	-	-	4
12	+	+	-	-	-	-	+	-	+	-	-	4

Table 3: Data of the employed EEG and MRI recordings

Subject	MRI description	Date of recording, MRI	Date of recording, 1 <sup>st</sup> EEG	Date of recording, follow-up EEG	Time difference between MRI- and 1 <sup>st</sup> EEG-recording (months)	Time difference between 1 <sup>st</sup> EEG- and follow-up EEG-recording (months)
1	unremarkable	07/2006	01/2007	01/2010	6	36
2	unremarkable	02/2007	01/2007	09/2013	1	80
3	unremarkable	06/2010	02/2010	02/2014	4	48
4	unremarkable	11/2010	02/2011	11/2013	9	33
5	unremarkable	05/2006	09/2006	01/2011	4	52
6	unremarkable	07/2008	09/2006	06/2010	22	45
7	unremarkable	12/2006	03/2007	04/2008	16	13
8	unremarkable	02/2008	02/2008	01/2014	0	71
9	unremarkable	12/2005	05/2007	06/2009	17	25
10	unremarkable	07/2010	10/2011	07/2012	15	9
11	unremarkable	05/2010	08/2012	01/2014	27	17
12	unremarkable	04/2010	07/2007	02/2011	45	43

## 2.2 EEG: RECORDING AND PREPROCESSING

Two EEG-recordings during physiological sleep were retrospectively chosen per patient: EEG 1, showing the maximum expression of the CSWS pattern, and EEG 2, recorded during a follow up period of three years and showing an improvement or even disappearance of the CSWS pattern.

The Spike and Wave Index (SWI) was calculated for each recording. A segment of all these recordings, with a preferable continuous and bilaterally expressed CSWS in EEG 1, was then taken for the further DICS and RPDC analysis.

To reduce subjective selectivity bias, all of the selection process was carried out by two experienced neurophysiologists.

For the recording IT-Med-System (Schreiber and Tholen Medizintechnik GmbH) was used. Sintered Ag/AgCl ring electrodes with built-in 5 kOhm resistors were positioned in sense of the 10-20-system using the Easy-cap (Falk-Minow Services, Herrsching-Breitbrunn, Germany). Discarding the ear-electrodes (A1, A2), two cheek-electrodes (F11, F12) were applied instead in addition to FC1, FC2, FC5, FC6, CP1, CP2, CP5, CP6, FT9, FT10, TP9, TP10, so that a 32-channel-EEG was formed. A sampling rate of 512 Hz was determined, and the filter properties were fixed to a time constant of 0,3 sec, an upper cutoff-frequency of 70 Hz and a lower cutoff-voltage of 10 $\mu$ V.

Using Cartool 3.51, each EEG-segment was cut to a length of 3 minutes and exported to the brain vision format (.eeg). The raw-data was opened with Analyzer 2.0 and converted to a mat-lab-file for further analysis.

## 2.3 EEG: SPECTRAL ANALYSIS

Each 3-min-EEG-segment was sampled at a rate of 512 Hz and was then divided into 1-sec-high-quality-epochs. These 1-sec-high-quality-epochs were selected 50% overlapping according to the Welch-Method (Gross et al., 2001) and were then windowed in the time domain.

The segmented and windowed signal was then discrete-Fourier-transformed to convert the EEG-signal from the time to the frequency domain (Muthuraman et al., 2008). The requirements for a discrete Fourier-Transformation are fulfilled, as an EEG-signal is both linear and discrete.

The squared magnitude of the result was computed and time-averaged to obtain the power-spectrum (synonymous: autospectra (Moeller et al., 2013)) (array of power measurement vs frequency) for each electrode. Containing the power contributed to the EEG-signal by the single frequencies, the frequency-band of 1-4 Hz was revealed as the most powerful for CSWS. This frequency-band served as the frequency-constraint in the source analysis.

The linear interaction between each pair of electrodes was presented as a cross-spectral-density-matrix, forming the basis for the following source analysis (Gross et al., 2001).

## 2.4 MRI: SELECTION AND PREPROCESSING

A routine-T1-MRI was chosen for each patient. With MRIcro ([www.mricro.com](http://www.mricro.com), version of 17<sup>th</sup> December 2009) all MRIs were reviewed to assure a sufficient amount of slices in all dimensions (sagittal, coronal and axial). If this requirement was not fulfilled, the MRI was discarded.

If there was more than one MRI available for the same patient, the one temporarily closest to the EEG-recording was used. The median time difference between the image (MRI) and the functional data (EEG) was 15,25 months (0-42 months).

All of the MRIs were recorded with a 3-Tesla Philips Achieva 3.0T TX MRI system (Philips, the Netherlands) and were saved in the DICOM-format. For further processing this needed to be changed to SPM-Analyze volume format with MRIConvert 2.0 Rev. 235 (<http://www.softpedia.com/get/Science-CAD/MRIConvert.shtml>).

After the selection, the MRIs were cleaned using SPM 8 (Wellcome Trust Centre of Neuroimaging; <http://www.fil.ion.ucl.ac.uk/spm/software/spm8>), a Matlab-based software. We chose the function "light-clean" for RF (radio frequency)-inhomogeneity-correction. RF-inhomogeneity increases with the field strength of the MRI-machine (Cohen et al., 2000). It

should be noted that SPM8 was only employed to clean the MRIs and therefore to prepare them for an automatic segmentation process.

## 2.5 SOURCE ANALYSIS

In order to find the sources responsible for specific EEG-activity measured on the scalp two problems need to be solved (Elshoff et al., 2013).

On the one hand there is the forward problem, which can be solved creating a head model, which contains the information of how a dipole at a given position, orientation and strength in the brain propagates signals to the scalp (Michel et al., 2004, Muthuraman et al., 2014). (figure 3, left)

On the other hand there is the inverse problem, describing which source is the origin of the measured potentials on the scalp (Gross et al., 2001).

### Forward Problem

The boundary element method (BEM) (Hamalainen and Sarvas, 1989) was used to calculate the numerical solution to the bioelectric forward problem. As a preparation for this method, the individual MRIs were segmented using a region growing method (Akalin-Acar and Gençer, 2004) as implemented in Curry 7 (<http://www.neuroscan.com/curry.cfm>).

The cleaned T1-MRIs were segmented into three compartments, which were non-intersecting, homogenous and isotropic: the skin, the skull and the brain (Muthuraman et al., 2014, Fuchs et al., 2002). First of all, an automatic segmentation process was run. To improve the accuracy of the 3D-head-model, as this in turn increases the accuracy of electromagnetic source imaging (Akalin-Acar and Gençer, 2004), this was followed by a manual correction by determining thresholds, spherical and vertical stop markers for the region growing process.

The different compartments are displayed as surfaces consisting of nodes forming abutting triangles (Fuchs et al., 2002). For all patients a high resolution was chosen, so that the number of nodes for all three surfaces averages 5000 and the number of triangles 10,000 in total (figure 3, right). The brain surface corresponds to the surface of the inner skull and defines the outer boundary of possible source localization. The within-lying volume is called the source space and is itself described by a 3D-grid with a spacing of 5 mm. The center of each voxel was defined as the origin of one current dipole.

The conductivity values for the three compartments were assumed to be 0,33 S/m for the skin and as well as for the brain and 0,0042 S/m for the skull (Fuchs et al., 2002).

Four fiducials (nasion, left and right preauricular points and inion) were determined (Fuchs et al., 2002) to fit the electrode positions to the image data. As the individual electrode positions were not registered during the EEG-recording, a standard 10-20 system was used. In all cases translational and rotational biases were reduced manually and it was ensured that all electrodes were placed tangential on the BEM-skin.

To compute the lead-field-matrix (LFM), and therefore the final head model, the processed image and functional data were combined. The LFM contains information about the geometry and conductivity of the individual head tissues, the electrode layout and the definition of the source space (Muthuraman et al., 2014, Michel et al., 2004).

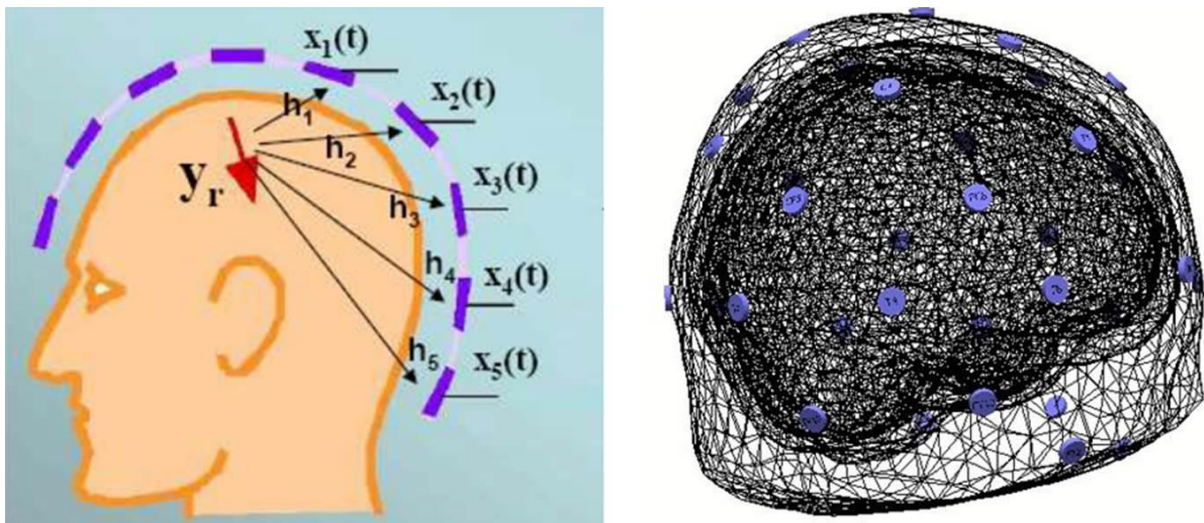


Figure 3: Forward problem. Left: a signal of a neural source of activity  $y$  at a position  $r$  is transformed by the conductivity model  $h$  to signal  $x$  on the scalp (Händel, 2010). Right: individual head model consisting of three non-intersecting spheres. The electrodes form a 10-20-system and are placed tangential on the BEM-skin.

### Reverse Problem

First of all the determination of a reference region is necessary to find coherent sources in the following analysis. Gross et al describe four different methods of finding a reference region (Gross et al., 2001). In this study the region with the highest field power for the given frequency was taken.

In order to find this most powerful region a powerspectrum was computed for every single voxel of the solution space based on the results of the LFM. As the signal-to-noise-ratio decreases with the depth of the brain (Van Veen et al., 1997), the reference region will always be located in cortical areas.

The coherence matrix ( $M(f)$ ) is estimated by computing the squared cross spectral density matrix ( $C_{xy}(f)$ ) between the reference region ( $x$ ) and all other voxels ( $y$ ) of the 3D-grid and

dividing it by the product out of the estimated autospectra of the reference region ( $C_{xx}(f)$ ) and the particular other voxel ( $C_{yy}(f)$ ). (Gross et al., 2001)

$$M(f) = \frac{|c_{xy}(f)|^2}{c_{xx}(f)c_{yy}(f)}$$

Coherence is a normalized measurement (Gross et al., 2005) and can therefore assume values between 0 (no coherence) and 1 (complete coherence) (Amjad et al., 1997). Once the voxel with the highest coherent value towards the reference region is found, it is projected out by being regarded as noise by the algorithm (Muthuraman et al., 2014). This enables the algorithm to find the next coherent source (Moeller et al., 2013). This procedure is repeated till the derived source does not reach the significance level anymore.

The significance of the sources was tested by a within subject surrogate analysis. The surrogates were estimated by a Monte Carlo random permutation 100 times shuffling of one second segments within each subject. The p-values were estimated for each of these random permutations and the 99<sup>th</sup> percentile of these p-values was taken as the significance level in each subject.

To define the spatial extent of each coherent source a regularization parameter  $\alpha = 0,001$  was determined, which has been shown to yield reliable results (Kujala et al., 2008).

Parallel to the coherent analysis, a linear transformation of the data was performed by using a linear constrained minimum variance spatial filter in the frequency band of 1-4 Hz (Moeller et al., 2013). It allows only passage of signals from specific locations and attenuates all signals originating from other locations (Muthuraman et al., 2008). This makes it possible to extract neural activity as an estimated individual time series for the single voxels of interest from the surface EEG (Muthuraman et al., 2008).

In order to get a pooled source signal estimate, taking into account all voxels contributing to one coherent source, all individual second order spectra were combined using a weighting scheme as described by Amjad et al (Amjad et al., 1997).

All these computations concerning the inverse problem have been done with Fieldtrip, a matlab based toolbox.

The individual maps of coherence were normalized and interpolated on the individual T1 MRIs in SPM8. To reduce subjective bias in interpretation of the source location, the MNI atlas, implemented in SPM 8, was used to name the corresponding brain regions.

This analysis was performed for each subject individually, followed by a group analysis, forming the grand average over all patients.



## 2.6 DIRECTIONALITY ANALYSIS

DICS characterizes the interaction between two processes in the frequency domain (Amjad et al., 1997) and reveals functional connectivity between them (Elshoff et al., 2013).

To achieve results about the effective connectivity and therefore about the direction of information flow between two signals, a tool based on Granger-causality named RPDC (renormalized partial directed coherence) was applied (Elshoff et al., 2013).

Granger causality is a stochastic theorem from 1969 and is based on the assumption that causes precede in time and increase the predictability of the incidence of their effects (Schelter et al., 2009).

In mathematical words: If linear prediction of  $X_{a(t+1)}$ , based on the past and present values of all variables but  $X_b$ , can be improved by adding the past and present values of  $X_b$ , then  $X_b$  Granger-causes  $X_a$ . (Schelter et al., 2009)

Partial directed coherence (PDC) is a concept introduced by Baccalá and Sameshima in 2001 and allows conclusions on interrelationships and causalities in multivariate systems by decomposing the ordinary coherence function into two directed coherences (Baccalá and Sameshima, 2001). But through the renormalization-process, which is run for RPDC, it can only take values between 0 and 1, emphasizing that a higher value indicates a stronger coupling, so a significance level and a confidence interval for the values can be calculated (Schelter et al., 2009).

A reverse source reconstruction is a condition precedent to apply the RPDC method to EEG data as it reduces the artifacts of volume conduction (Haufe et al., 2013). This was, in our study, guaranteed by using DICS-processed data.

The RPDC method applies a multivariate autoregressive modeling approach (MVAR) to obtain the autoregressive coefficients from the spatially filtered source signals in the frequency band of 1-4 Hz. This computation was carried through by using the open source matlab package ARFIT (Neumaier and Schneider, 2001). A precondition for obtaining these coefficients is the correct model order, which was estimated by the AIC (Akaike Information Criterion), a model selection method (Akaike, 1974).

To test the significance of the RPDC values and therefore the significance of each information flow, the significance level was first of all estimated by a surrogate analysis to establish a null distribution, with loss of all directionality and coherence of the original data (Haufe et al., 2013). The surrogate analysis was done by a bootstrapping method: The original time series was divided into one-second non-overlapping segments of equal size. These segments were shuffled randomly and put together again in this random order. This process was repeated 100 times and the 99<sup>th</sup> percentile was taken as the threshold of significance value (Kamiński et al., 2001).

In addition, significant connections were tested with a time inversion technique for EEG, which effectively makes the RPDC results robust to volume conduction artifacts (Haufe et al., 2013).

## 2.7 STATISTICAL ANALYSIS

For the statistical analysis of the data two computations were carried out:

The correlation index between the SWI on the one hand and the mean source power, the mean source coherence and the mean-RPDC-values on the other hand, calculated separately for the first and the second EEGs. As the data sets are of small size and a Gaussian distribution cannot be assumed, the Spearman rank correlation index ( $r_s$ ) was employed. This index is, in contrast to the Pearson's correlation coefficient, appropriate for non-normally distributed data and robust to data sets that may include outlier values. Being dimensionless, it varies from -1 (perfect negative correlation) over 0 (no correlation) to +1 (perfect positive correlation) (Mukaka, 2012).

$$r_s = 1 - \frac{6 \times \sum_{i=1}^n (d_i)^2}{n(n^2 - 1)}$$

$d$  describes the difference in rank between the two correlated variables.

Significance was tested afterwards with a significance level of  $p = 0,01$  with a null hypothesis that there is no association at all.

The other computation provides the test of significant difference in central tendency between EEG 1 and 2 for the mean absolute power, the mean source coherence and the mean RPDC-values. The Mann-Whitney-Test was employed as it does not include any distributional assumptions in contrast to the t-test, which demands normally distributed samples, but depends on homoscedasticity of two distributions (Skovlund and Fenstad, 2001).

A common rank order is built out of the two samples and the test-statistic  $U$  is computed for both samples using the following formula:

$$U_1 = n_1 \times n_2 + \frac{n_1(n_1 + 1)}{2} - T_1$$

$$U_2 = n_1 \times n_2 + \frac{n_2(n_2 + 1)}{2} - T_2$$

$T$  = rank-sum of the sample 1 respective 2 in the common rank. (Schwarz, 2010)

By discarding the 0-hypothesis that there is no difference in central tendency for one of the above mentioned three parameters in EEG 1 and 2 with  $p < 0,01$  a significant difference would be proven.

### **3 RESULTS**

#### **3.1 SPIKE AND WAVE INDICES**

The SWIs (spike and wave indices) of the EEGs, recorded during the active phase of CSWS, varied interindividually between 53 and 100% (mean 79,1%).

In the follow-up EEGs the patients can be divided into two subgroups: In four cases the sleep EEG has normalized completely (SWI = 0%). In the other 8 cases CSWS could still be monitored. But only one of those 8 patients (patient11) worsened, all the others showed an improvement with an SWI-value ranging from 2-94 % (mean 31%), which can be considered a significant improvement. (table 4)

#### **3.2 DICS (DYNAMIC IMAGING OF COHERENT SOURCES)**

First EEG (figures 4, 5 and 6)

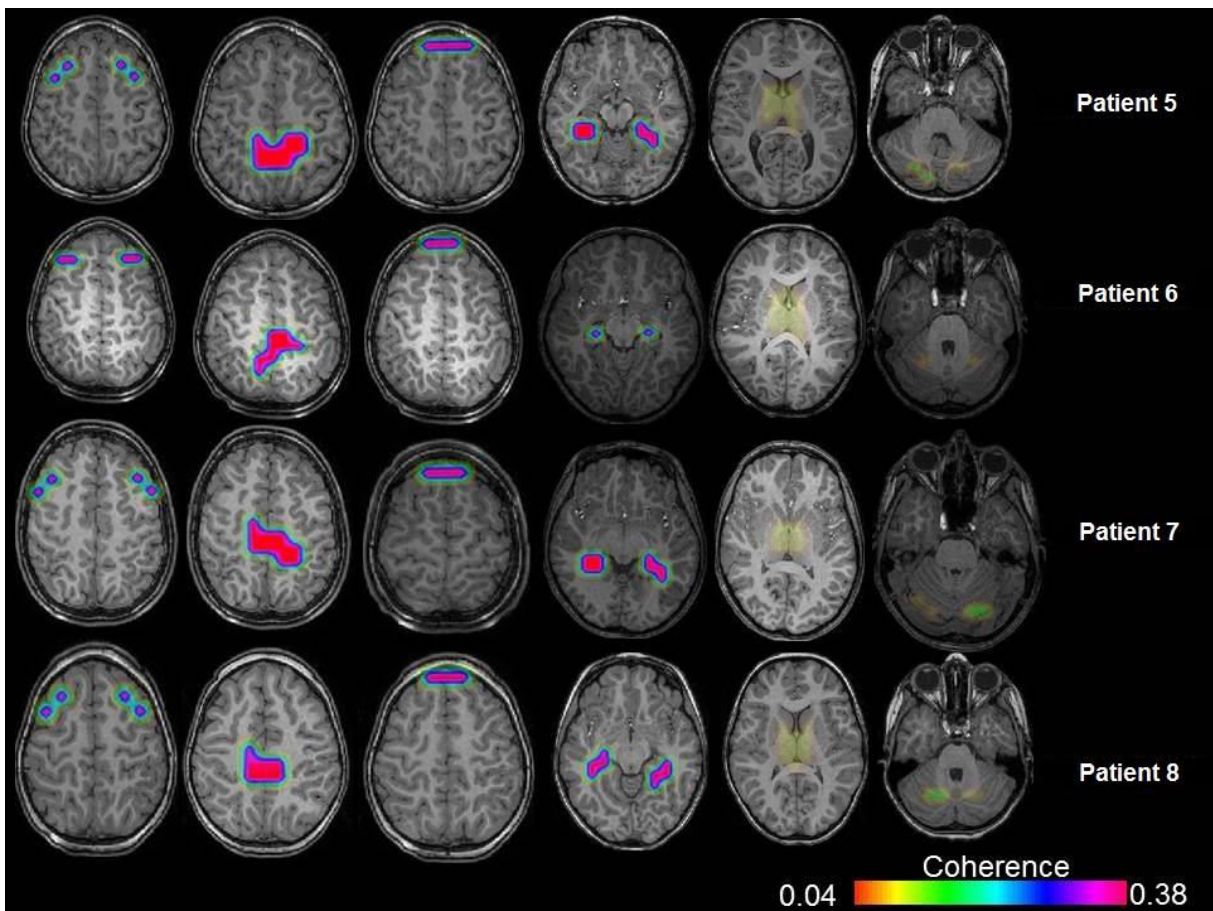
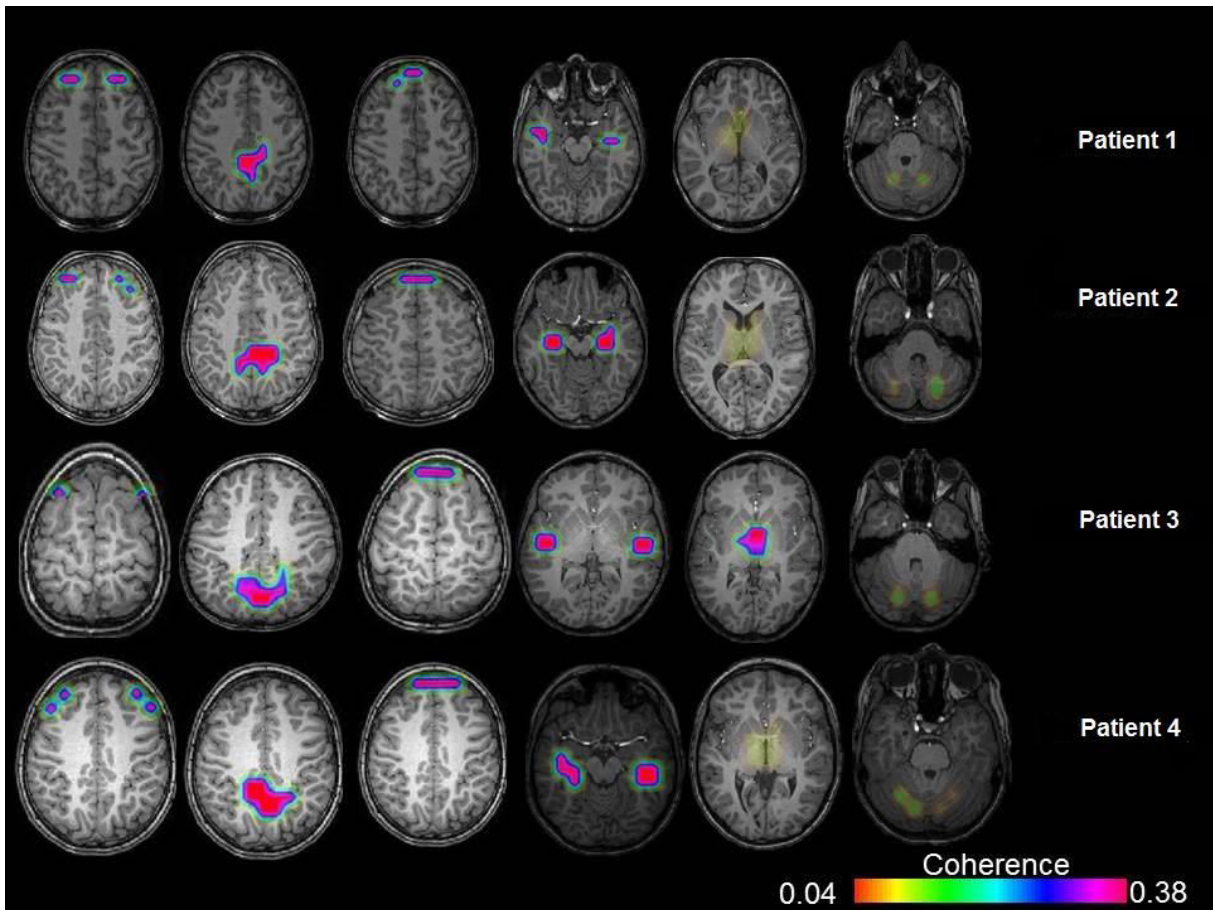
All sources shown are statistically significant with  $p = 0,003$ . The source with the strongest power is located in the medial prefrontal gyrus in all cases. Defining this as the reference region, 5 coherent sources are revealed and will be named in the following in the order of decreasing coherence value, ranging from 0,04 to 0,38.

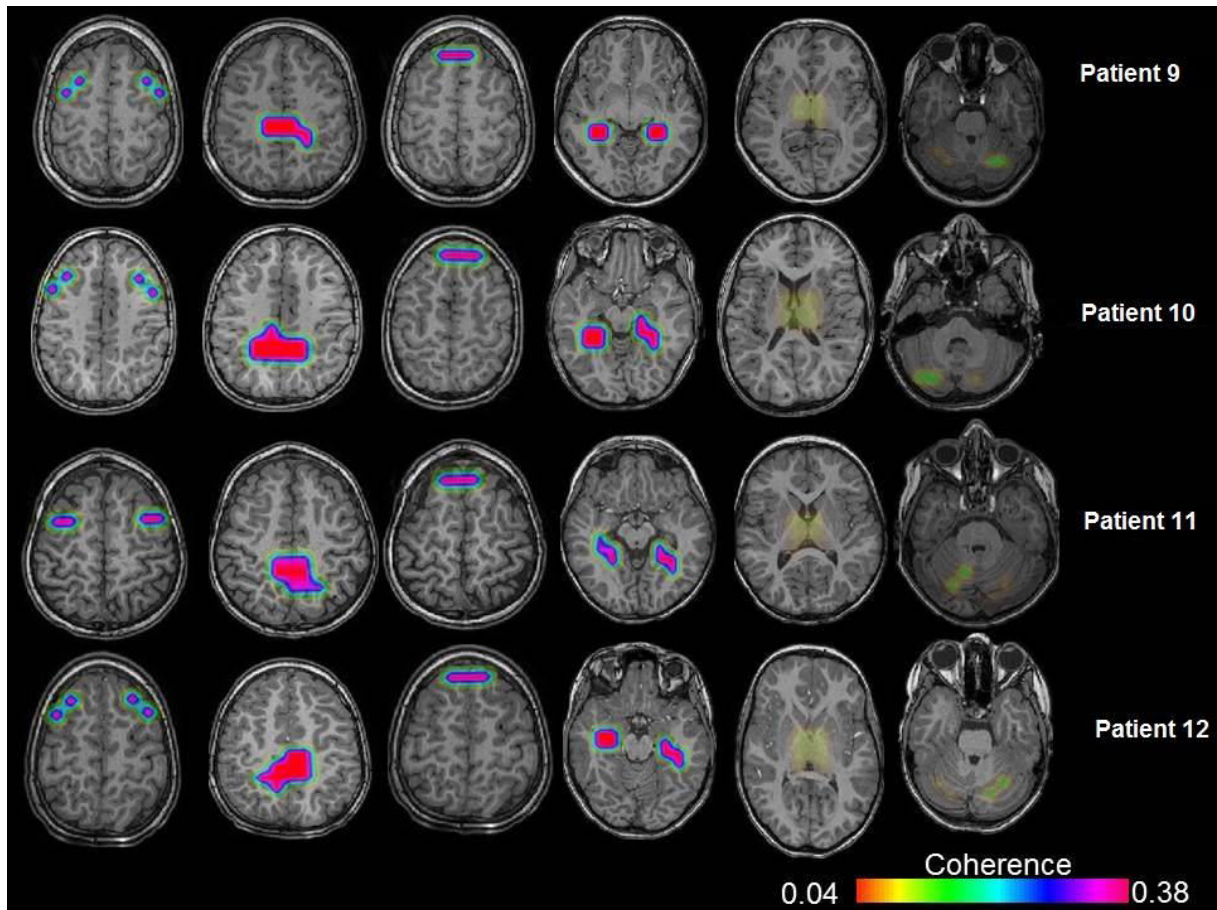
The first coherent source, and therefore the second source in total, is located in the posterior cingulate cortex in 8 cases and in the somatosensory association cortex (BA 7) in 4 cases. (table 4)

The third source is found in the dorsolateral prefrontal gyrus (BA 9) equally in all patients.

The fourth source on the other hand varies in its location interindividually: In 6 cases it is detected in the medial temporal gyrus (BA 21), in 5 cases in the parahippocampal gyrus (BA 34) and in one case in the insular cortex. (table 4)

The fifth and the sixth source are again consistent in all patients and are traced in the medial thalamus (BA 23) and in the cerebellum.





Figures 4, 5 and 6: Individual DICS-results of the 1<sup>st</sup> EEG-recordings of all patients. On the left hand side, the most powerful source, the medial prefrontal gyrus, is found in all cases. Also the third source, identified as the dorsolateral prefrontal gyrus, the fifth, located in the medial thalamus, and the sixth source, found in the cerebellum are identical in all 12 cases.

Table 4: Defining the location of the 2<sup>nd</sup> and the 4<sup>th</sup> source for each patient. PCG – posterior cingulate cortex, SSAC – somatosensory association cortex, MTG – medial temporal gyrus, PHG – parahippocampal gyrus, IC – insular cortex. No correlation can be found between the number of impairments and the development of the electroencephalographic appearance.

Subject	2 <sup>nd</sup> Source	4 <sup>th</sup> source	SWI 1 <sup>st</sup> EEG (%)	SWI 2 <sup>nd</sup> EEG (%)	Comparison of the two EEGs	Number of Impairments
1	PCG	MTG	65	46	improved, continuous frontal spikes	6
2	SSAC	PHG	65	0	improved	6
3	PCG	IC	59	5	improved, isolated spikes	4
4	PCG	MTG	86	2	improved, isolated spikes	7
5	PCG	MTG	67	0	improved	7
6	PCG	PHG	89	15	improved, isolated spikes	5
7	SSAC	MTG	74	37	improved, short periods of diffuse CSWS	4
8	SSAC	MTG	68	0	improved	6
9	SSAC	PHG	100	0	improved	8
10	PCG	MTG	97	15	improved, isolated spikes	9
11	PCG	MTG	85	99	worsened, diffuse CSWS	4
12	PCG	PHG	53	19	improved, short periods of diffuse CSWS	4

### Follow up EEG

Regarding the DICS-results of the follow-up EEGs, two groups of patients can be differentiated: The ones with a normalized sleep-EEG (first group, SWI = 0%, 4 patients) and the ones with a persistent CSWS-pattern, overriding the severity of its occurrence (second group, SWI > 0%, 8 patients).

In the first group the source of strongest power is located in the somatosensory association cortex/ precuneus and only 2 statistically significant coherent sources are detected, without interindividual differences in location and with coherence values between 0,03 and 0,18. (figure 7)

The first coherent source is found in the medial prefrontal cortex and the second one in the dorsolateral prefrontal cortex. Neither subcortical nor temporal sources could be revealed in contrast to the network of the first EEG.

The DICS-results of the second group can be superposed on the results of the first EEG as no differences can be detected (figures 8 and 9). In this case the coherence values vary between 0,06 and 0,38.

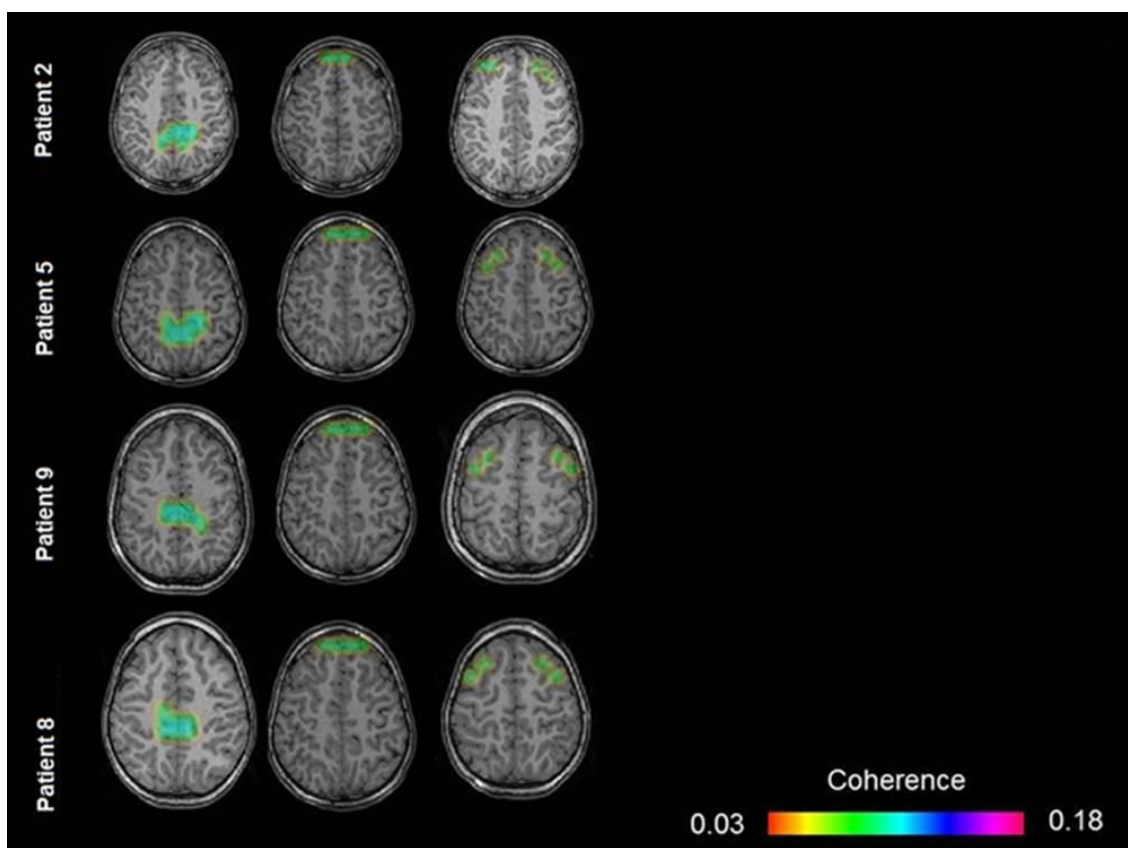
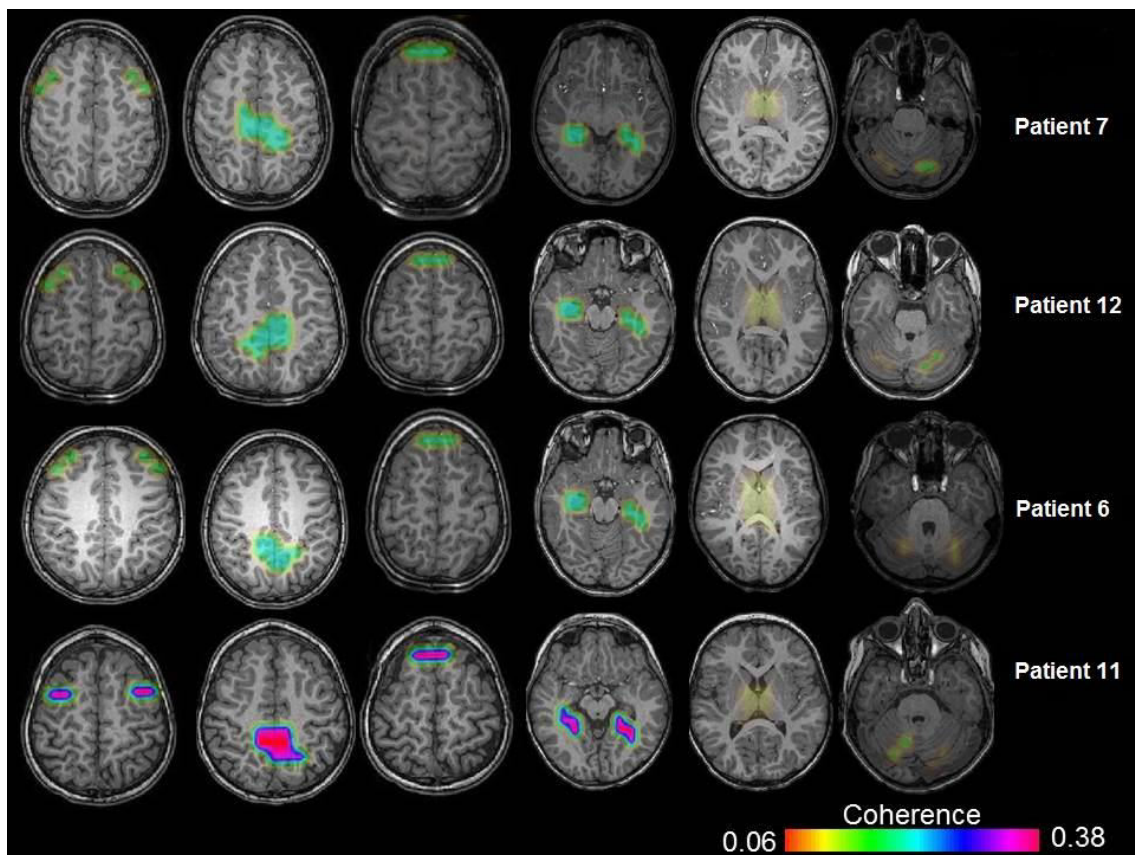
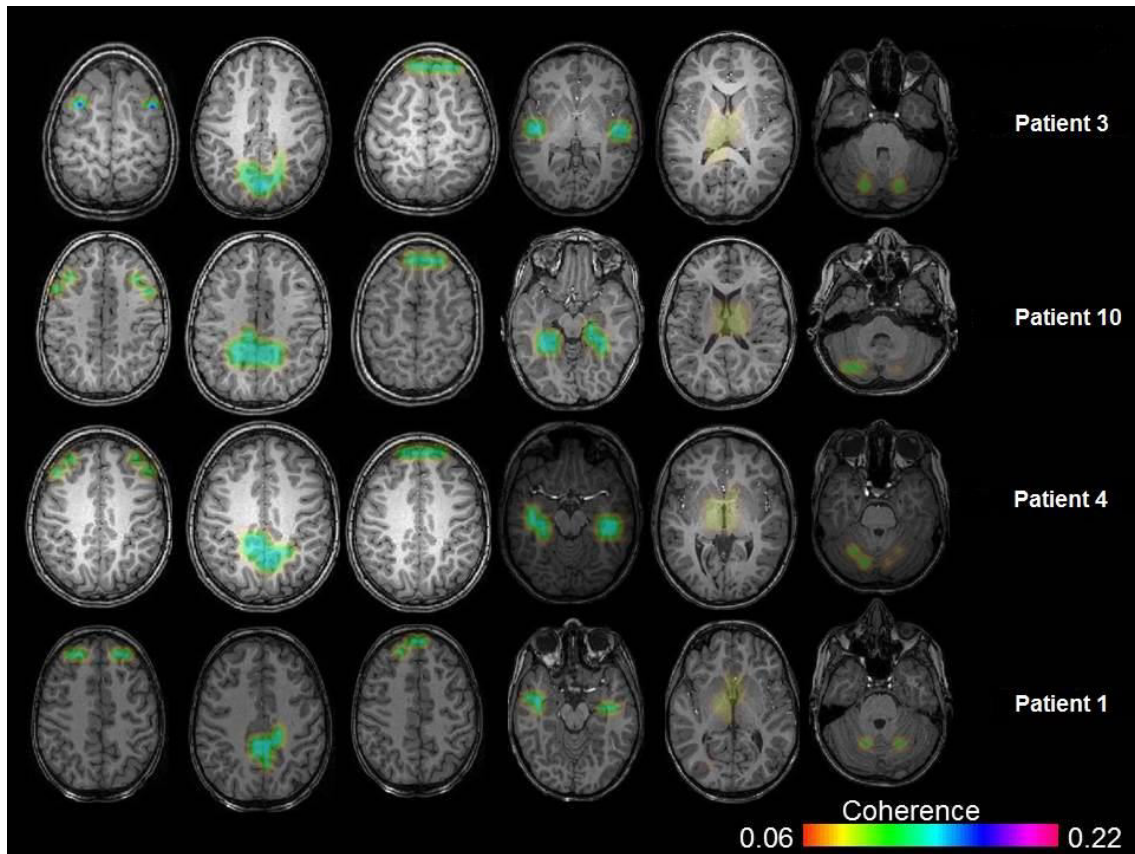


Figure 7: DICS results of the follow-up EEG-recordings. Only the patients with a SWI of 0% are displayed. The network just consists of 3 significant sources, non of them located subcortical.



Figures 8 and 9: DICS results of the follow-up EEG-recordings. Only the patients with a SWI of  $> 0\%$  are displayed. The location of the sources can be superposed on the results of the 1<sup>st</sup> EEGs.

### 3.3 RPDC (RENORMALIZED PARTIAL DIRECTED COHERENCE)

#### First EEG

Regarding the results of the effective connectivity between the sources by applying RPDC, only a group analysis was carried out and only statistically significant connections between the sources are considered in this description and are displayed in figure 10.

The information flow between the sources can be divided into uni- and bidirectional ones.

A central figure of the network consists of a thalamocortical circuit built up by sources 2, 4 and 5. The strongest information flow is found from source 2 (parietal region) to source 4 (temporal region). The medial thalamus can be considered as the central hub of this figure, sending information towards source 4 and being connected to source 2 in a bidirectional way.

In addition, the thalamus exchanges information with the cerebellum and thereby represents the only linkage to the sixth source in the whole network.

From source 2 (parietal region) the information flow continues to the anterior regions. At first it reaches source 1, the medial prefrontal cortex, and then continues to the dorsolateral part of this region.

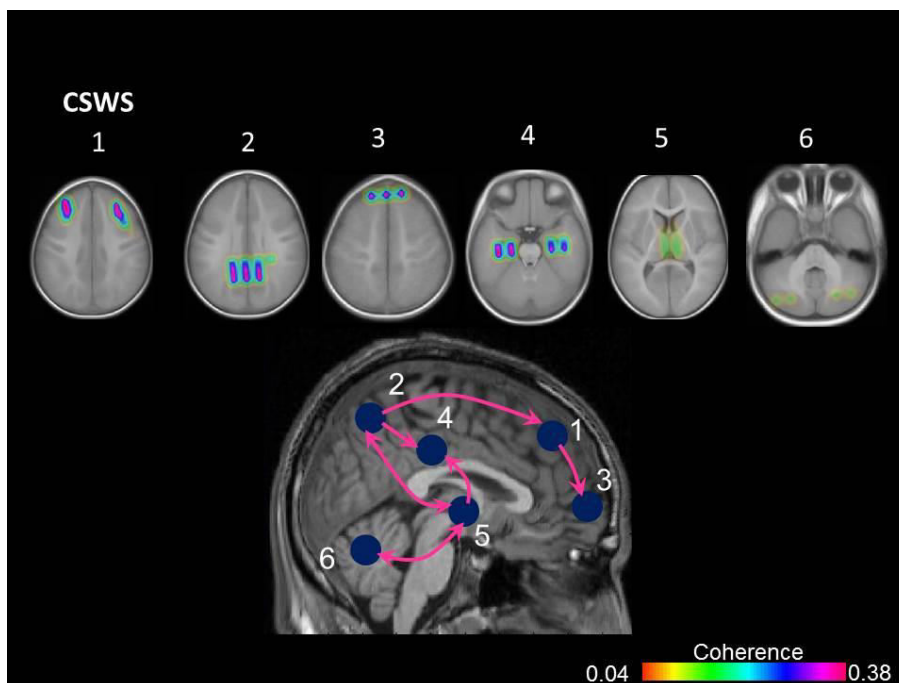


Figure 10: The upper part of the figure shows the group analysis of the DICS-results of the 1<sup>st</sup> EEG recordings. The lower part shows the RPDC results and therefore the effective connectivity between the sources. A thalamocortical circuit builds up a central hub with a bidirectional information flow towards the cerebellar source and a unidirectional flow towards the prefrontal region.



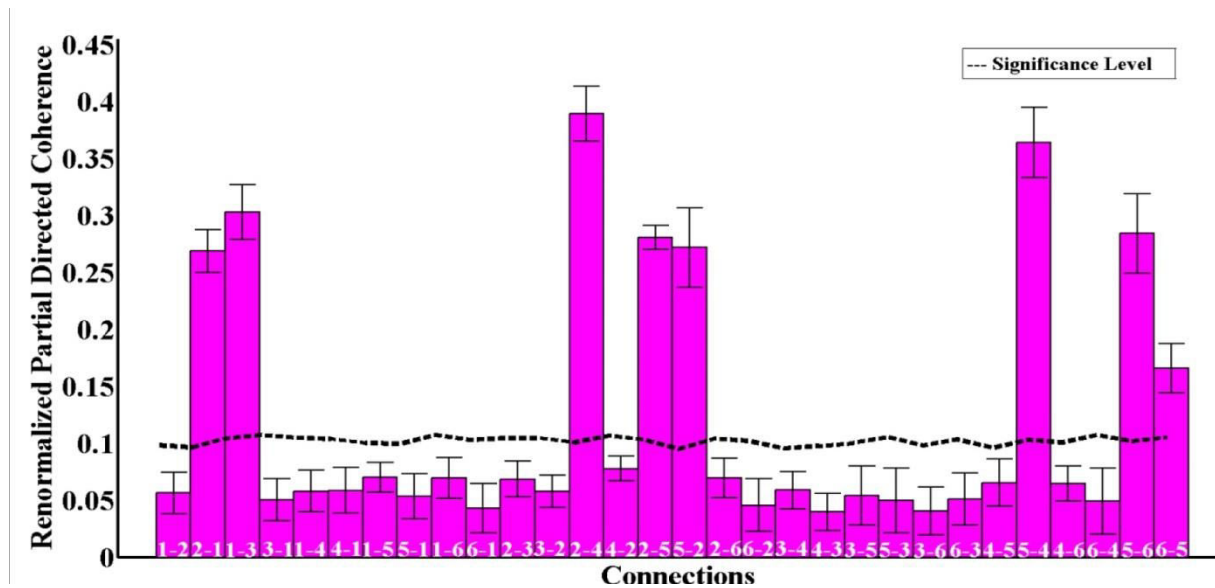


Figure 11: An RPDC value was computed for every possible connection between the six sources. The significance level of those connections is displayed as a dotted line and was derived by a surrogate analysis.

#### Follow up EEG

Again the two groups of patients as mentioned above can be differentiated.

In the group of patients with a SWI of 0% only two significant connections can be detected: The information flow starts in the first source and continues towards the second and finally the third. A bidirectional linkage between the sources could not be revealed. (figure 12)

In the results of the other 8 patients (persisting CSWS in the follow up EEG) no difference can be found compared to the results of the first EEG. (figure 13)

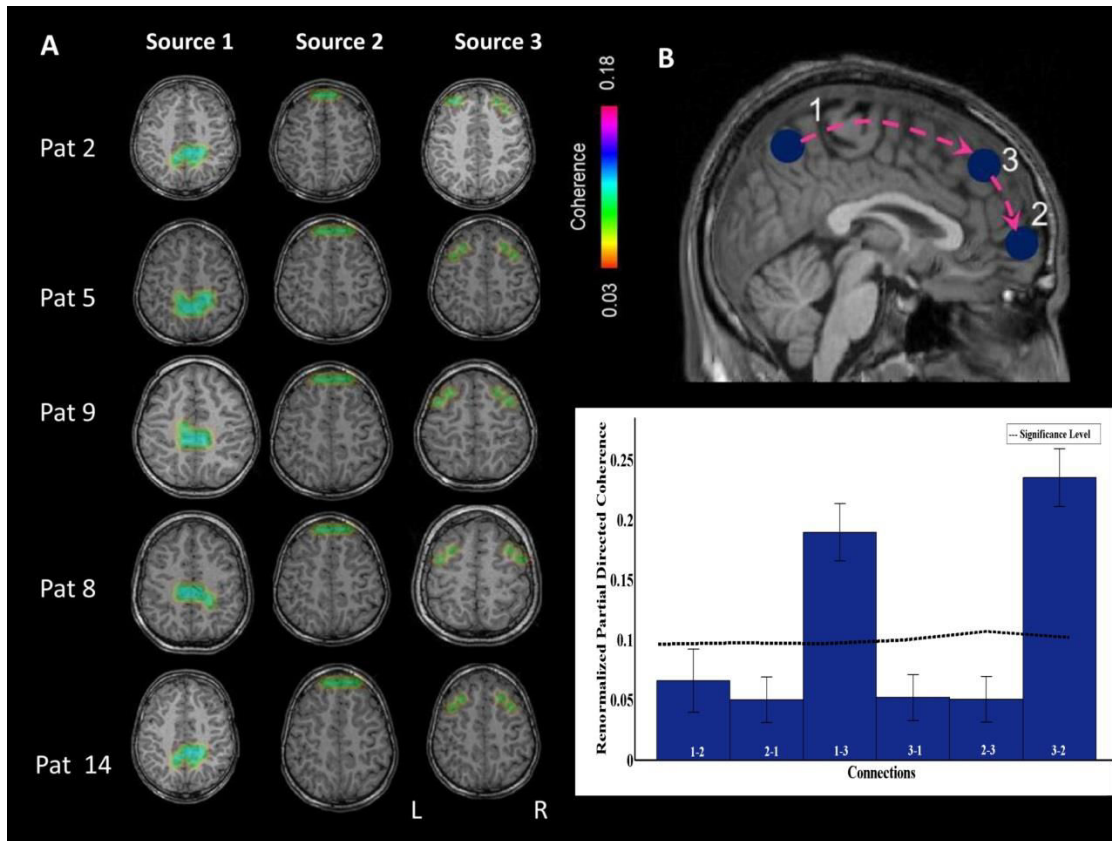


Figure 12: The RPDC results of the follow-up group with a SWI of 0% are displayed. Only a unidirectional information flow from the somatosensory association cortex/precuneus towards the prefrontal region can be regarded significant.

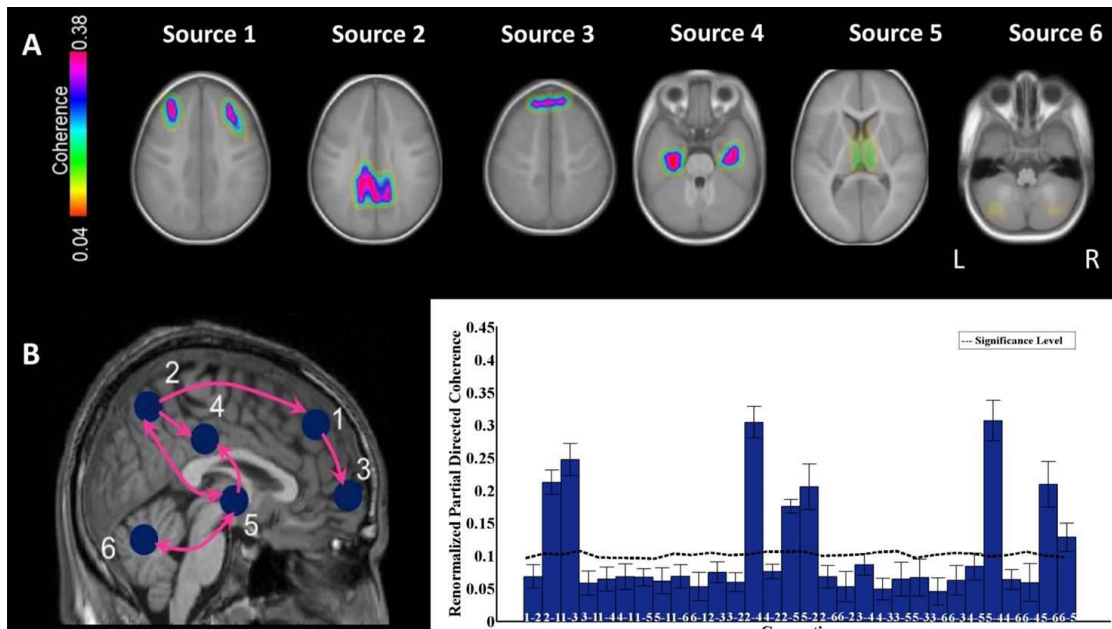


Figure 13: The RPDC results of the follow-up group with a SWI of > 0% are displayed. There are only differences in the RPDC-values of the effective connections compared to the results of the 1<sup>st</sup> EEG. But the network with a central thalamocortical circuit and a bidirectional linkage with the cerebellum and a unidirectional one towards the prefrontal region stays the same.

### 3.4 SPIKE AND WAVE INDEX AND ITS CORRELATIONS

The respective spike and wave index of each patient was correlated with the mean absolute source power, the mean coherence strength and the mean RPDC strength. These computations were carried out for two sets of data, the ones of the first (figure 14) and the ones of the follow up EEG (figure 15) resulting in 6 graphs.

All of them show a strong linear correlation between the SWI and the other parameters in both data sets. The correlation index varies between  $r = 0,45$  (absolute source power, follow up EEG) and  $r = 0,71$  (source coherence strength, first EEG) and tested significant in all six cases with p-values varying from 0,003 to 0,009.

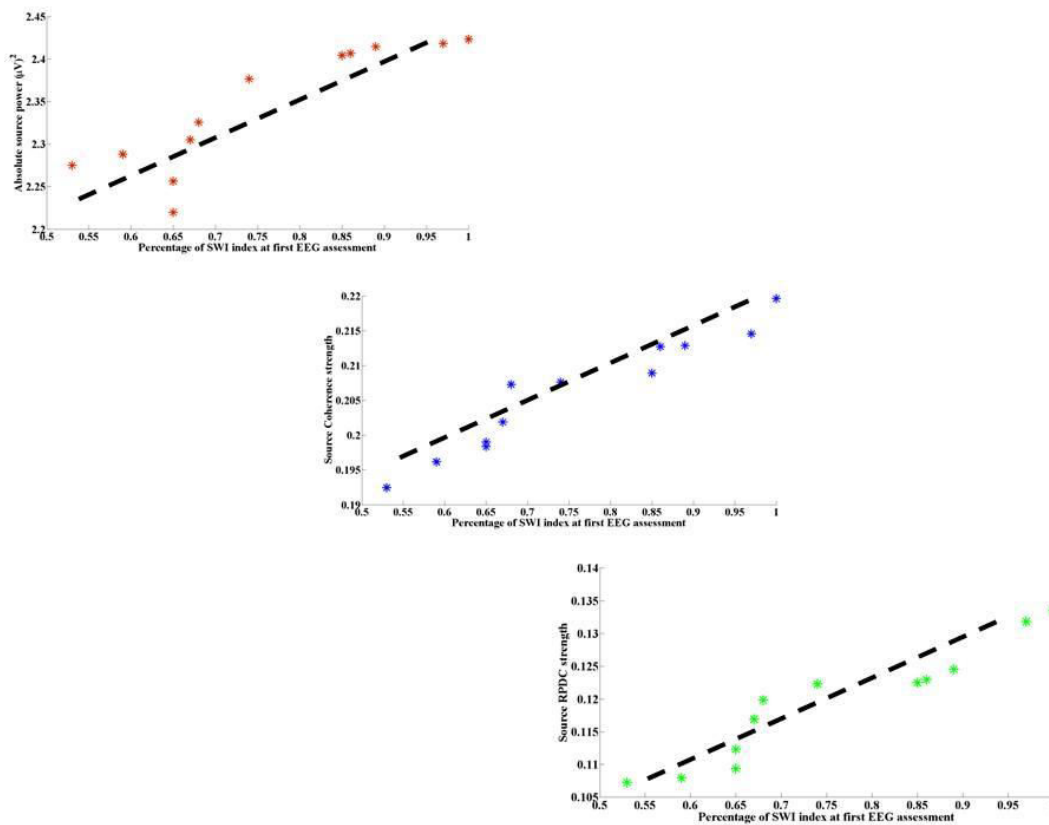


Figure 14: Plotting the SWI of the 1<sup>st</sup> EEG on the x-axis against the values of the absolute source power, respectively the source coherence strength and the source RPDC strength, on the y-axis reveals a linear correlation in all three cases.

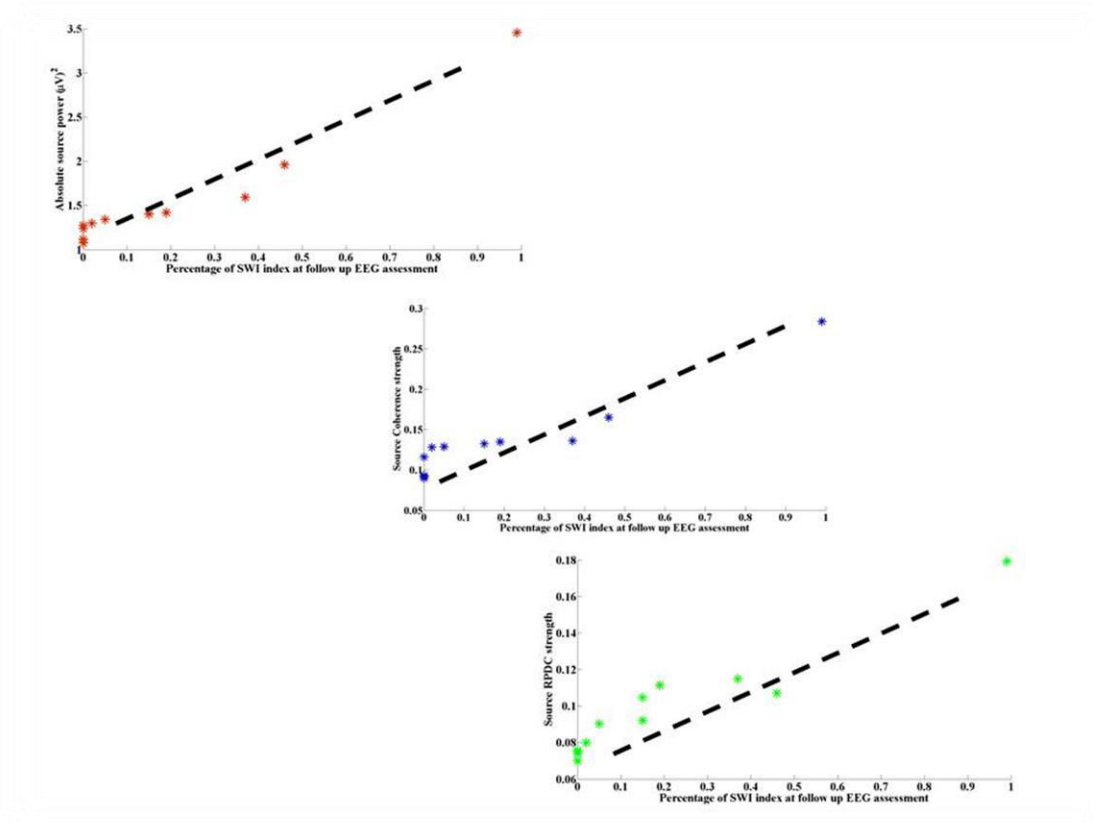


Figure 15: Plotting the SWI of the follow-up EEG on the x-axis against the values of the absolute source power, respectively the source coherence strength and the source RPDC strength, on the y-axis reveals a linear correlation in all three cases.

## 4 DISCUSSION

### 4.1 DISCUSSION OF METHODS

Michel et al point out that there are four main factors influencing the accuracy of source analysis: the number and position of electrodes, the head model, the inverse model applied and the SNR (signal-to-noise-ratio) (Michel et al., 2004).

In this study a number of 32 electrodes was chosen. Although Michel et al described a drastic increase in localization precision using 63 instead of 31 electrodes (Michel et al., 2004), a simulation study by Moeller et al could find a big improvement in accuracy from 16 to 32 channels but not anymore from 32 to 64 (Moeller et al., 2013).

In addition, one has to take into account, that a low SNR in an EEG-recording is one of the main problems and the SNR decreases with the number of electrodes. The number of electrodes is therefore a trade-off between spatial precision and noise. But comparing those two effects, the precision suffers more from the noise than from less electrodes (Michel et al., 2004). To increase the SNR even more, long segments of the sleep EEGs with a duration of 3 minutes were analyzed.

To assure an even distribution of the electrodes on the scalp the Easy-Cap was employed during the EEG-recording. Michel et al call it sufficient to reconstruct the position of electrodes by applying landmarks to the head-model to reduce rotational and translational bias as it was done in this study (Michel et al., 2004). But accuracy could still be improved by also recording the exact coordinates of each electrode instead of employing a standard 10-20-system.

Concerning the head model, it was used an individual one rather than a spheric model used in other studies, which was often named as a limitation factor of the methods (Japaridze et al., 2013, Moeller et al., 2013). But again an increase of precision in source localization could be achieved by recording the image and the functional data temporarily closer to each other, as growing up in the meantime can add a bias to the results.

In literature it was long debated if DICS can reveal deep brain structures in a source analysis (Gross et al., 2001). The fact that it is possible was first only shown in MEG-studies with the detection of sources for example in the thalamus, the brainstem, the basal ganglia and the cerebellum (Timmermann et al., 2003, Schnitzler et al., 2009, Gross et al., 2001, Südmeyer et al., 2006) but recently also in EEG-studies (Japaridze et al., 2013, Japaridze et al., 2015, Moeller et al., 2013). This inverse solution can therefore be considered a powerful method to

map epileptic activity (Moeller et al., 2013), especially if a high SNR can be assured (Muthuraman et al., 2014).

## 4.2 DISCUSSION OF RESULTS

By specifically looking at the frequency band of 1-4 Hz we are analyzing the background activity in the sleep-EEGs, i.e. the delta oscillations, underlying the resting state activity during sleep of CSWS patients. The network revealed by DICS consists of the medial prefrontal gyrus, the posterior cingulate cortex/ the somatosensory association cortex, the dorsolateral prefrontal cortex, the middle temporal gyrus/ the parahippocampal gyrus/ the insular cortex, the medial thalamus and the cerebellum. Therefore it aligns with the group results of other neuroimaging studies, especially the ones published by De Tiège, Siniatchkin and Ligot.

De Tiège et al emphasize the importance of distant connected areas and point out that not only the epileptic foci are responsible for the neurophysiologic impairment but also their impact on the function of other areas by surrounding or remote inhibition (De Tiegge et al., 2009, De Tiegge et al., 2008). This theory is underlined by Ligot et al who could observe a prolonged hypometabolism in such areas still in the awake state of the patients (Ligot et al., 2014).

The children suffering from CSWS often show impairments in short-term memory and attention and stand out by aggressive, hyperactive or autistic-like behavior.

Areas typically engaged with the working memory are the dorsolateral prefrontal cortex, the cerebellum and the parietal lobules (Passamonti et al., 2011, Barber et al., 2013, Emond et al., 2009, Van Overwalle et al., 2015, Stoodley, 2012). Memory encoding and retrieval is associated with the parahippocampal gyrus. It is also known that the abilities of the working memory interrelate proportionally to the strength of connection between the anterior and posterior components of the DMN (default mode network) (Castellanos et al., 2008), in our case the altered connection between source 3 and source 1.

Aggressive behavior corresponds to a lack of inhibiting inappropriate emotions and impulses, which is controlled by the prefrontal cortex (Arnsten, 2009); the affect in general can be linked to the ventromedial part of this brain area, source 1 in our study (Arnsten and Rubia, 2012).

Attention-deficit and hyperactivity are key symptoms of ADHD (attention deficit hyperactivity disorder). The prefrontal cortex is involved in screening distractions and allocating, sustaining and shifting attention in a task-appropriate manner (Arnsten, 2009), so that atypical prefrontal, but also cerebellar, activity lead to familial vulnerability for ADHD (Mulder et al., 2008). Emond et al suggest that poor behavioural inhibition can be considered the central

problem of this syndrome (Emond et al., 2009) and cognitive and inhibitory control are encoded in the dorsolateral prefrontal cortex (source 3) (Arnsten and Rubia, 2012). Especially a lack of connectivity to the dorsal parts of the DMN, the precuneus and the posterior cingulate cortex, is found in patients suffering from ADHD but also in patients with autistic-like disorders (Castellanos et al., 2008, Barber et al., 2013).

Cheng et al describe neuronal key systems associated with autism: The middle temporal gyrus, which is involved in theory of mind processing and included in facial expression, shows an increased connectivity towards the medial thalamus. On the other hand, the precuneus must be mentioned, which shows a reduced functional connectivity (Cheng et al., 2015). Another area included in emotional responses and empathic processes is the insula (Menon and Uddin, 2010).

Although a clear relation can be seen in the explanations above, one has to take into account that behavior is not only caused by a neuronal network underlying CSWS but also by the results and side effects of drug treatment, social integration, self-confidence and excessive demands through the environment.

Summarizing the neuronal areas mentioned in context with the behavioral impairments, it is obvious that the key nodes of the DMN, the ventromedial prefrontal cortex, the posterior cingulate cortex, the precuneus, the lateral parietal cortex, the parahippocampal gyrus and the middle temporal lobe (Castellanos et al., 2008, Parks and Madden, 2013, Uddin et al., 2011) play an outstanding role both for the clinical symptoms and for the neuronal network underlying the delta activity during sleep of CSWS patients like already described in previous studies (Ligot et al., 2014, Siniatchkin et al., 2010, De Tiege et al., 2013). In addition, it is suggested that alterations in the DMN contribute to the pathogenesis of ADHD, Alzheimer, schizophrenia, autism and depression (Siniatchkin et al., 2010, Castellanos et al., 2008). The DMN is a late maturing network (Uddin et al., 2011), active during the resting state of the brain (Rubia, 2013). Its activity is therefore anti-correlated to attentional networks. The function of the DMN is internally-oriented and contributes to cognitive control and self-referential memory. On the other hand, an appropriate response towards external events demands a suppression of the DMN (Parks and Madden, 2013). This suggests a dependence of its activity on the state of consciousness and may explain the generalization and enhancement of epileptic activity during sleep.

Another system which builds up the central hub in the network according to our results is the thalamocortical one. As pointed out in the introduction, this system is confronted with the least input of afferences during non-REM sleep, creating a basis for increased synchronized activity in a 3 Hz-frequency (Klinke, 2009). Siniatchkin et al even call the involvement of the thalamocortical network unequivocal, considering the association of CSWS with the non-REM sleep (Siniatchkin et al., 2010). Disregarding the state of consciousness, the

thalamocortical loop is known to be predisposed to synchronized discharges during epileptic activity. It is often recruited by the initial cortical epileptic focus in the process of secondary generalization (Neubauer et al., 2014). This accords with the thalamus only appearing in the source analysis in case of generalized seizures like absences (Moeller et al., 2013).

It is also assumed that the cerebellum, our sixth source, controls the occurrence of generalized spike-and-wave-discharges and is able to disrupt thalamocortical activity patterns in general. (Kros et al., 2015) This makes the cerebellum a potent modulator of epileptic activity.

Integrating all that information, the thalamocortical network, together with the cerebellum are the areas recruited or even responsible for generalized epileptic activity. This goes along with our findings in the follow-up EEGs: The patients with persisting CSWS still show the same network seen in the first EEG, but the ones with a SWI of 0% only show cortical sources and especially no cerebellar and thalamical involvement anymore.

After having had a closer look at the pathophysiology of the neuropsychological impairments, now the influence of sleep and the general pathophysiology of epileptic activity and age-dependence as other striking specifications of CSWS are to be focused.

In the introduction it has already been indicated that a maturing brain is more vulnerable to epileptic discharges. Late steps of brain maturation include a segregation process between and an integration process within large scale neuronal networks (Uddin et al., 2011, Parks and Madden, 2013). Again it is the DMN which is one of those late maturing and reconfigured networks (Barber et al., 2013, Uddin et al., 2011): The connectivity between the anterior and posterior parts, meaning between the medial prefrontal cortex and the posterior cingulate cortex increases with age (Rubia, 2013, Barber et al., 2013), exactly the connection between source 3 and 1 which plays a big role in the pathogenesis of ADHD and autism, as explained above. In addition, it is suggested that the task-related activity of the DMN decreases with progressing brain maturity, which goes along with a segregation process from the CEN (central executive network), which can be considered the antagonist of the DMN (Uddin et al., 2011, Rubia, 2013).

Finally, by finding a strong linear correlation between the SWI, considered to be an indicator for the severity of CSWS, on the one hand and parameters of this study, the absolute source power, the coherence strength and the RPDC strength, on the other hand, the three latter can be consulted to estimate the severity as well.



## 5 CONCLUSION

The study shows one more time that DICS is a powerful technique for source analysis based on EEG-data.

The revealed sources are concordant to the results of EEG-fMRI- and PET-studies, especially regarding the detection of the key nodes of the DMN and the thalamus as a central hub. In addition, parallels can be found to sources known to be responsible for the development of related psychiatric disorders and the pathogenesis of epileptic activity in general.

With the disappearance of CSWS the network underlying the delta activity during sleep also changes from involvement of the thalamus and other subcortical structures to an exclusively cortical network. As we found a linear relationship between the SWI on the one hand and the mean absolute source power, the mean coherence strength and the mean RPDC strength on the other hand, the three last-mentioned parameters seem to be appropriate to estimate the severeness of CSWS.

## 6 SUMMARY

CSWS is an age-related epileptic encephalopathy consisting of the triad of seizures, neuropsychological impairment and a specific EEG-pattern. This EEG-pattern is characterized by spike-and-wave-discharges emphasized during non-REM sleep. Until now, little has been known about the pathophysiologic processes. So far research approaches on the underlying neuronal network have been based on techniques with a good spatial but poor temporal resolution like fMRI and FDG-PET.

In this study the search for sources participating in the neuronal network of CSWS is done by processing EEG-data, with high temporal resolution. This allows not only interferences on the location of the individual sources but also on the direction of information flow between them. DICS is applied to the data to solve the inverse problem in the frequency domain. After finding the most powerful source in the given frequency range, significant coherent areas are computed to form the network. Afterwards RPDC, based on Granger causality, is implemented to reveal effective connectivity between the sources.

12 patients suffering from CSWS without any proof for macroscopic cerebral pathologies in a T1-MRI were investigated at two points of time, before and after treatment.

All results are compared to other studies on the neuronal network of CSWS, to knowledge about genesis of epileptic activity in general and to knowledge about the pathogenesis of related psychiatric syndromes.

During the active phase of CSWS the thalamus represents the central hub of the neuronal network, being part of a thalamo-cortical network including also the cerebellum and key nodes of the DMN. Therefore the results are concordant to the ones of former studies and to assumptions on the genesis of epileptic activity. Also the enhancement during non-REM sleep can be well explained. In addition, pathogenetic parallels are found to autism, ADHD and memory-impairment.

After cessation of CSWS, the network consists of exclusively cortical sources.

In addition to the SWI the mean absolute source power, the mean coherence strength and the mean RPDC strength could be revealed as reliable indicators for the severity of the encephalopathy.

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## **8 APPENDIX**

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