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Objective EEG Bed Side Assessment of Impaired Conscious Awareness in Epilepsy

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1.) Aim of this study

Recent studies were able to show that epileptic seizures with simultaneous loss of consciousness affect large parts of cortical and subcortical networks. This has consequences for people suffering from epilepsy. However, it is not possible to objectively measure consciousness in some kind of bedside test. This study's aim is to develop a test that can measure and classify loss of consciousness using electroencephalography (EEG) close to the patient.

In previous projects in Frankfurt within the same scientific research group, sleep was used as a model for loss of consciousness to identify spatial and temporal neural correlates via functional magnetic resonance imaging (fMRI). In this follow-up study, the investigation group tries to use these findings to determine neural signals of consciousness reduction using EEG alone. Afterwards, we want to develop and use a quantitative EEG analysis as a clinical test for the reduction of consciousness.

2.) Preliminary work

2.1 Epilepsy and reduced consciousness

Epilepsy has a high prevalence and can sometimes go ahead with severe health restrictions in everyday life. These limitations also have socio-economic consequences that should not be underestimated (Newton & Garcia, 2012). Impairment of consciousness plays a major role in this. Especially in idiopathically generalized epilepsy (IGE) in children and adolescents as well as temporal lobe epilepsy (TLE) in adults, there is a decrease in consciousness (Blumenfeld, 2011). This has a strong impact on the lives of patients and covers all areas of everyday life, such as work, social interactions and driving vehicles. The International League against Epilepsy (ILAE) already proposed a change of the guidelines in the classification of epilepsy in 2014 in response to the increasing relevance of the topic and last implemented them directly in the guidelines (Blumenfeld & Meador, 2014; Fisher et al., 2017). Over the past years, pathophysiological issues of awareness loss have been studied and associated activity patterns of cortical and subcortical regions have been identified.

2.2 This study's relevance

The cognitive limits of patients with epilepsy may differ in quality and strength, but also in appearance. Thus, several research groups have already shown that a reduction in consciousness can also occur interictal (Aarts, Binnie, Smit, & Wilkins, 1984; Berman et al., 2010; Binnie, 2003; Blumenfeld, 2012; H Laufs & Duncan, 2007; Helmut Laufs, 2012; Helmut Laufs, Lengler, Hamandi, Kleinschmidt, & Krakow, 2006; Pressler, Robinson, Wilson, & Binnie, 2005). The development of an objective test procedure, which could also be used in outpatient care, could be able to show cognitive impairment even interictal and therefore help to optimize the handling of the disease. Potential side effects due to drug treatment could be better evaluated and interpreted as part of a risk-benefit assessment. Furthermore, the planned test procedure could prevent focusing too much on a healthy EEG signal or the

number of epileptic seizures as a treatment target (Besag, 1995; Binnie, 2003). Accordingly, we would be able to improve the quality of life in epilepsy patients and possibly prevent further progression of the disease's consequences (Bertram, 2007). Better assessment of driving ability would also be of relevance. Psychometric scales have already been proposed in the measurement of ictal consciousness, but these are based on retrospective self-assessment or the assessment of a third person (Nani & Cavanna, 2014). Unfortunately, these indirect measurements cannot guarantee unrestricted objectivity and reproducibility. The planned test procedure based on the physiological measurements of the EEG could solve this problem.

3.) Hypotheses

The aim of this study is the development of an objective and reproducible clinical test, which can quantify and classify consciousness based on EEG data. First, we want to develop an EEG-based application for measuring impaired consciousness in wakefulness and sleep. This application should be developed based on the aforementioned previous fMRI-based study (E. Tagliazucchi et al., 2013). Our first hypothesis is that temporal integrity decreases from wakefulness to light sleep, as being a marker of consciousness and attention. This already has been shown in the previous studies using fMRI (E. Tagliazucchi et al., 2013; Enzo Tagliazucchi et al., 2013; Enzo Tagliazucchi, Crossley, Bullmore, & Laufs, 2016; Enzo Tagliazucchi & Laufs, 2014). Processing a microstate analysis of the EEG data, we could display sequences in topographic maps and measure temporal integrity using appropriate parameters (Brodbeck et al., 2012; Kuhn et al., 2015).

Furthermore, the planned EEG data sample will be compared to already given fMRI analysis data by source analysis. In this context it is hypothesized that EEG-modularity and temporal integrity will be higher comparing EEG data on wakefulness to the data during sleep.

As an additional goal it is planned to apply the developed analysis / the findings from the aforementioned hypothesis (wakeful vs. sleep) on epilepsy patients as well as on non-sufferers (epilepsy vs. non-epilepsy). The microstate sequences, potentially showing an impaired temporal integrity – could be used as a marker for impaired consciousness in pathological circumstances. It is hypothesized that the temporal integrity of the microstate sequence will be decreased in patients with epilepsy and impairment of consciousness.

In a third step the spatial and temporal analysis of our EEG data will be applied on the pathological EEGs, got from patients suffering from epilepsy. A higher modularity and a lower temporal autocorrelation in epilepsy patients compared to controls are expected. For the analysis EEG data which was acquired during a wakeful rest will be used.

4.) Study design

Each participant will be studied like followed.

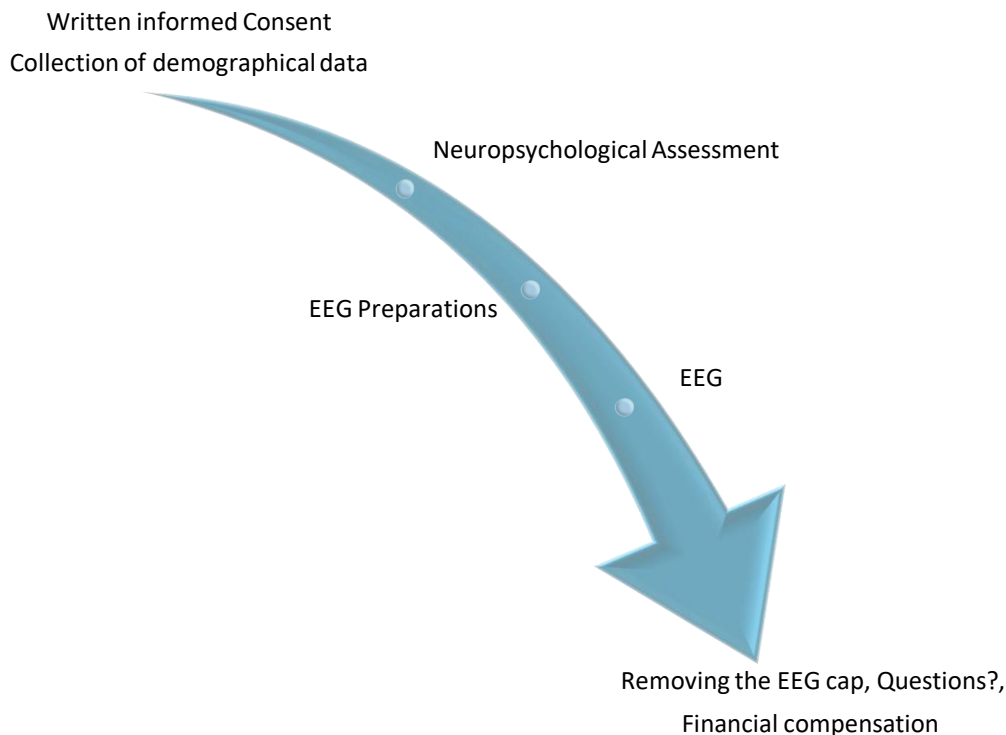


Image 1: study design in „Objective bed side assessment of impaired conscious awareness in epilepsy“

5.) Description

5.1 Course

After proving their suitability for participation in the study, participants will be informed about the aim, potential risks as well as about the time course and the scientific background of this project. Afterwards, demographic data will be collected and a neuropsychological assessment will be carried out. In addition to the neuropsychological test procedures, which register the cognitive domains of memory, attention, concentration and executive functions, clinical questionnaires and general psychosocial measures are collected (Table 1).

All of the subsequently named tests will take place in a safe environment for patients and participants and will be conducted by a trained psychologist. A clinician scientist will always be there on demand.

Afterwards, the EEG electrodes will be placed and prepared for the following recordings. The EEG will be conducted by trained staff. After finishing the recordings, the cap will be removed and participants will have the opportunity to wash and dry their hair as well as asking any questions about the procedure. After finishing the data collection financial compensation will be paid.

Table 1: Psychological Tests

Neuropsychological tests	Clinical surveys	Psychosocial disposition
<ul style="list-style-type: none"> - Verbal learning- and memory test - Short term memory and visuo-constructive skills: Rey Complex Figure Test - Attention and executive functions: Test of Attentional Performance (TAP) - Working memory: Repeating Numbers from Wechsler Adult Intelligence Scale; Block-Tapping-Test 	<ul style="list-style-type: none"> - Depression: Beck Depression Inventory-II - Anxiety and Depression: Hospital Anxiety and Depression Scale - Psychopathologies: Symptom checklist-90-S 	<ul style="list-style-type: none"> - Sleep Habits: The Pittsburgh Sleep Quality Index PSQI - Quality of Life: The German version of the Quality of Life in Epilepsy Inventory - Consciousness: retrospective quantitative consciousness assessment in epilepsy seizures: The Ictal Consciousness Inventory

5.2 Potential risks and side effects of EEG measurement

As a health risk to fetuses cannot be completely ruled out, women who could be pregnant will not take part in the study.

In the context of EEG recordings, incidental pathological findings can occur, for example in the form of epilepsy-typical patterns. Therefore, the possibility of pathological findings is mentioned in the declaration of consent, which has to be read and signed by every participant. In the case of incidental findings, the participant will be informed and will have the opportunity of an appointment with a physician in our outpatient clinic.

By using CE-certified electrode caps and devices from 'Brainproducts' as required, EEG recordings do not represent a risk for participants.

While recording EEG, a medical doctor will be there on demand or will even stay during the measurement, even if there is no increased risk for epileptic seizures due to the data collection.

6.) Ensuring security for participants

6.1 Recruiting epilepsy patients

The recruitment of study participants with IGE and TLE will take place in the outpatient department of the Department of Neurology (University Hospital) in Kiel. If the patients are suitable for participation in the study, the treating physicians will inform them about the study procedure. If patients are interested in participating, they can contact the investigation staff, ask further questions and potentially register to participate. Furthermore, resident neurologists will be informed about the study and will be asked to pass the study information on to suitable patients by giving them flyers. A third possibility of recruiting could be to contact the Group "Epilepsie Kiel e.V.", who could publish information about this study on their website.

6.2 Recruiting the control group

Participants will be informed about the study by postings / flyers, laid out in the Christian-Albrechts University in Kiel, the University Hospital Schleswig-Holstein in Kiel, the polytechnic Kiel as well as in the adult education center. For the control group we would like to expand the recruiting about a posting in eBay Kleinanzeigen.

6.3 In- and exclusion criteria

In the group of epilepsy patients, severe secondary diseases lead to exclusion from the study. For the control group, only healthy, age-adjusted subjects will be included. Further exclusion criteria are systemic diseases of the central nervous system, addictions and other serious psychiatric illnesses. An existing pregnancy also leads to exclusion from the study.

6.4 Termination criteria

Upon request, the examination can be paused or terminated at any time. Furthermore, the attending physician can stop the continuation of the examination if the subject is at risk. If the subject stops the participation, no explanation is required and there will not be any disadvantages.

7.) Sample size calculation

The planned sample size is mainly based on the abovementioned EEG-fMRI study (Tagliazucchi et al., 2013). There, 63 healthy subjects were surveyed and divided into 4 groups according to sleep stages. Due to possible technical problems and artifacts, individual subjects can be excluded, especially in the group of patients. In order to achieve a sufficient effect, 30 subjects per group will be collected (IGE, TLE, healthy controls).

8.) Time course

Data acquisition will take about 20 months with 2 to 3 appointments per week. For the following analysis 16 months are planned.

9.) Analysis

Before the statistical analysis of the data, EEG raw data will be preprocessed. The programs MatLab®, Cartool and BrainVision Analyzer for which licenses are not necessary or already available at the institute, will be used for this. The data from the psychological testing, questionnaires and, demographical data will be analyzed in R statistics or / and Jupyter Notebooks.

10.) Data acquisition, transfer and storage

The data acquisition takes place in the abovementioned institute. The long-term storage of the data takes place on an external storage medium that is stored under lock in the institute. Personal data and the provided pseudonymized data are stored separately from one each

other, so that an assignment to one another is only possible via a key list that is only known to the project manager and the involved staff. The original survey material is also archived under lock and without the possibility of personal identification. The data is archived for 10 years in accordance with current regulations.

Literature

- Aarts, J. H. P., Binnie, C. D., Smit, A. M., & Wilkins, A. J. (1984). Selective cognitive impairment during focal and generalized epileptiform eeg activity. *Brain*, 107(1), 293–308. <https://doi.org/10.1093/brain/107.1.293>
- Berman, R., Negishi, M., Vestal, M., Spann, M., Chung, M. H., Bai, X., ... Blumenfeld, H. (2010). Simultaneous EEG, fMRI, and behavior in typical childhood absence seizures. *Epilepsia*, 51(10), 2011–2022. <https://doi.org/10.1111/j.1528-1167.2010.02652.x>
- Bertram, E. (2007). The relevance of kindling for human epilepsy. *Epilepsia*. <https://doi.org/10.1111/j.1528-1167.2007.01068.x>
- Besag, F. M. C. (1995). The therapeutic dilemma: Treating subtle seizures or indulging in electroencephalogram cosmetics? *Seminars in Pediatric Neurology*, 2(4), 261–268. [https://doi.org/10.1016/S1071-9091\(95\)80005-0](https://doi.org/10.1016/S1071-9091(95)80005-0)
- Binnie, C. D. (2003). Cognitive impairment during epileptiform discharges: Is it ever justifiable to treat the EEG? *Lancet Neurology*. [https://doi.org/10.1016/S1474-4422\(03\)00584-2](https://doi.org/10.1016/S1474-4422(03)00584-2)
- Blumenfeld, H. (2011). Epilepsy and the Consciousness System: Transient Vegetative State? *Neurologic Clinics*. <https://doi.org/10.1016/j.ncl.2011.07.014>
- Blumenfeld, H. (2012). Impaired consciousness in epilepsy. *The Lancet Neurology*. [https://doi.org/10.1016/S1474-4422\(12\)70188-6](https://doi.org/10.1016/S1474-4422(12)70188-6)
- Blumenfeld, H., & Meador, K. J. (2014). Consciousness as a useful concept in epilepsy classification. *Epilepsia*, 55(8), 1145–1150. <https://doi.org/10.1111/epi.12588>
- Brodbeck, V., Kuhn, A., von Wegner, F., Morzelewski, A., Tagliazucchi, E., Borisov, S., ... Laufs, H. (2012). EEG microstates of wakefulness and NREM sleep. *NeuroImage*, 62(3), 2129–2139. <https://doi.org/10.1016/j.neuroimage.2012.05.060>
- Fisher, R. S., Cross, J. H., French, J. A., Higurashi, N., Hirsch, E., Jansen, F. E., ... Zuberi, S. M. (2017). Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*, 58(4), 522–530. <https://doi.org/10.1111/epi.13670>
- Kuhn, A., Brodbeck, V., Tagliazucchi, E., Morzelewski, A., von Wegner, F., & Laufs, H. (2015). Narcoleptic Patients Show Fragmented EEG-Microstructure During Early NREM Sleep. *Brain Topography*, 28(4), 619–635. <https://doi.org/10.1007/s10548-014-0387-1>
- Laufs, H. (2012). Functional imaging of seizures and epilepsy: evolution from zones to networks. *Current Opinion in Neurology*, 25(2), 194–200. <https://doi.org/10.1097/WCO.0b013e3283515db9>
- Laufs, H., & Duncan, J. S. (2007). Electroencephalography/functional MRI in human epilepsy: what it currently can and cannot do. *Curr Opin Neurol*, 20(4), 417–423. <https://doi.org/10.1097/WCO.0b013e3282202b92>
- Laufs, H., Lengler, U., Hamandi, K., Kleinschmidt, A., & Krakow, K. (2006). Linking generalized spike-and-wave discharges and resting state brain activity by using EEG/fMRI in a patient with absence seizures. *Epilepsia*, 47(2), 444–448. <https://doi.org/10.1111/j.1528-1167.2006.00443.x>
- Nani, A., & Cavanna, A. E. (2014). The quantitative measurement of consciousness during epileptic

seizures. *Epilepsy and Behavior*. <https://doi.org/10.1016/j.yebeh.2013.09.007>

Newton, C. R., & Garcia, H. H. (2012). Epilepsy in poor regions of the world. *The Lancet*, 380(9848), 1193–1201. [https://doi.org/10.1016/S0140-6736\(12\)61381-6](https://doi.org/10.1016/S0140-6736(12)61381-6)

Pressler, R. M., Robinson, R. O., Wilson, G. A., & Binnie, C. D. (2005). Treatment of interictal epileptiform discharges can improve behavior in children with behavioral problems and epilepsy. *The Journal of Pediatrics*, 146(1), 112–7. <https://doi.org/10.1016/j.jpeds.2004.08.084>

Tagliazucchi, E., Crossley, N., Bullmore, E. T., & Laufs, H. (2016). Deep sleep divides the cortex into opposite modes of anatomical–functional coupling. *Brain Structure and Function*, 221(8), 4221–4234. <https://doi.org/10.1007/s00429-015-1162-0>

Tagliazucchi, E., & Laufs, H. (2014). Decoding Wakefulness Levels from Typical fMRI Resting-State Data Reveals Reliable Drifts between Wakefulness and Sleep. *Neuron*, 82(3), 695–708. <https://doi.org/10.1016/j.neuron.2014.03.020>

Tagliazucchi, E., von Wegner, F., Morzelewski, A., Brodbeck, V., Borisov, S., Jahnke, K., & Laufs, H. (2013). Large-scale brain functional modularity is reflected in slow electroencephalographic rhythms across the human non-rapid eye movement sleep cycle. *NeuroImage*, 70, 327–339. <https://doi.org/10.1016/j.neuroimage.2012.12.073>

Tagliazucchi, E., von Wegner, F., Morzelewski, A., Brodbeck, V., Jahnke, K., & Laufs, H. (2013). Breakdown of long-range temporal dependence in default mode and attention networks during deep sleep. *Proceedings of the National Academy of Sciences*, 110(38), 15419–15424. <https://doi.org/10.1073/pnas.1312848110>