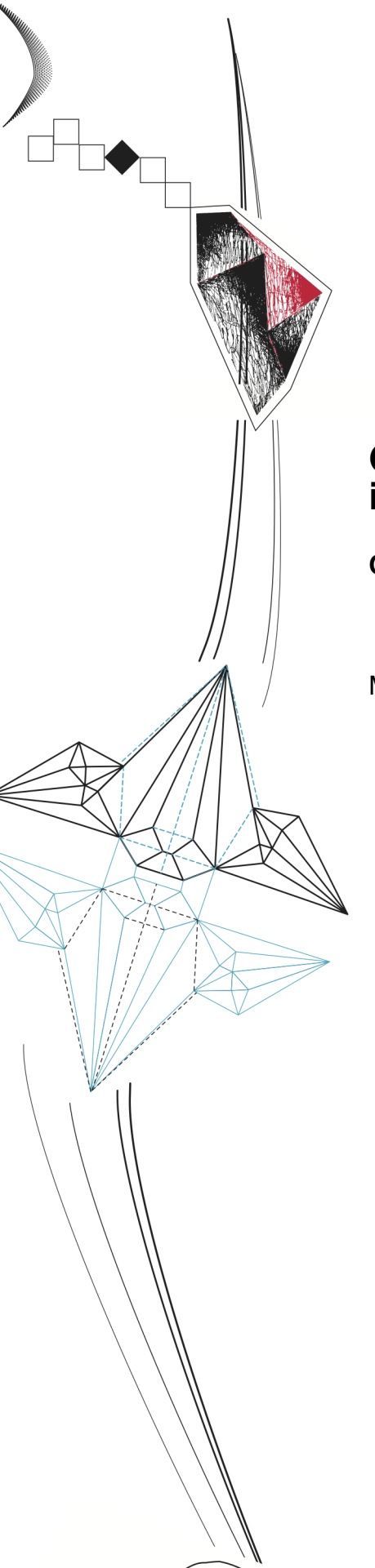

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Master Thesis Technical Medicine

Observations on suppressed power following single pulse electrocortical stimulation

CLINICAL RELEVANCE FOR THE REC2STIM TRIAL

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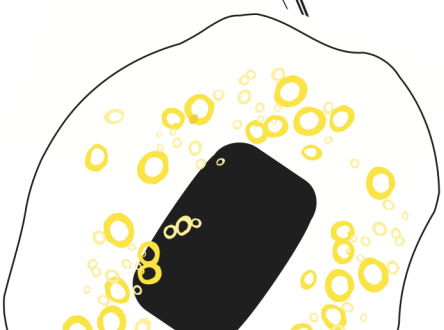

UMC Utrecht

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Preface

Zes jaar en 1 maand later; het einde van een periode als Technische Geneeskunde student. De afgelopen 12 maanden heb ik stagegelopen op de afdeling Functionele Neurochirurgie en Epilepsie in het UMC Utrecht. Een afdeling waar ik na een eerdere stage van 10 weken graag terugkeerde. De enthousiaste groep mensen maakte dat ik mij hier erg thuis voelde. Hierdoor heb ik met veel plezier aan mijn masterthesis gewerkt. Bij deze wil ik jullie bedanken.

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Mijn (ex) kamergenoten; Emile, Daniël, Banu, Nicole, Lieke, Matteo en Erik-Jan, bedankt voor de altijd ontspannen sfeer en gezelligheid tijdens het werken. Emile, jouw onuitputtelijk bron van raadsels waren een zeer welkome afleiding. Ook Willemiek, Tineke, Jurgen, Sandra, Cyrille en Maeike bedankt voor de gezellige momenten tijdens onder andere de lunch.

Als laatste wil ik ook mijn (schoon)familie en vrienden bedanken. In het bijzonder mijn ouders en zusje, bedankt voor jullie interesse en vertrouwen. En natuurlijk Leon, bedankt voor je luisterend oor op de momenten dat het allemaal even tegenzat en vertrouwen dat alles goed kwam.

Michelle

Summary

Purpose: Central lobe epilepsy (CLE) is a focal epilepsy arising from the pre- and/or postcentral gyrus, and is by nature often medically refractory with a high seizure frequency. Surgery is not an evident treatment due to the high risk of contralateral sensorimotor impairment, related to excision of eloquent cortex. Recently, a trial for a new therapy for CLE patients has been proposed: Rational Extra-Eloquent Closed-loop Cortical Stimulation (REC2Stim) using electrical stimulation within a local epileptogenic network to abort the build-up towards a seizure. The stimulation location is preferably connected to the seizure onset zone (SOZ), but outside eloquent cortex. Single pulse electrical stimulation (SPES) is often used to identify the SOZ based on delayed responses (DRs), but can also expose the underlying connections based on early responses (ERs). In time-frequency decompositions of SPES, suppression of power for frequencies $<$250 Hz is sometimes observed after stimulation. We hypothesized that power suppression after SPES might serve as a surrogate marker for suppression of epileptiform activity and could be a preferred site of cortical network stimulation. As ERs can identify cortical connections and were sometimes co-observed with the suppressions, we explored whether this suppressed power (SP) was associated with the occurrence of ERs and therefore, a direct connection between cortex underneath the stimulus pair and response electrode. Furthermore, we explored whether timing of the stimulation and thus the phase of the background electrocorticography (ECoG) signal determines the occurrence of an SP.

Method: Refractory epilepsy patients who underwent intracranial subdural electrocorticography monitoring at the UMC Utrecht were retrospectively analysed. SPES (10 pulses: 0.2 Hz, 1 ms, 4-8 mA) was routinely administered on adjacent electrode pairs. A machine learning algorithm (support vector machine (SVM)) was developed to detect SP based on features 'area' and 'duration' (chapter 2). ERs and SP were detected and visually checked in a total of 34600 responses across ten subjects. Six subjects had (one of) their grids implanted in the central lobe. The other four subjects had grids implanted elsewhere. We determined the number of response electrodes in which both ER and SP, either ER or SP, and neither ER nor SP were evoked by the same stimulus pair. A chi-squared test was used to determine whether SP was associated with the occurrence of ERs (chapter 3). The relevance of the phase of the ECoG signal at the moment of stimulation for the occurrence of power suppression was researched with the inter trial coherence (ITC) and instantaneous phase between stimuli with a suppression (chapter 4).

Results: Ten subjects were included (four females, median age 15, range 9-41 years). In all subjects, the number of response electrodes with SP was smaller than those with ERs. All subjects considered, 8% of the responses contained both ER and SP, 16% had an ER without SP, 3% had an SP without an ER and 73% had neither ER nor SP. In each subject, significantly more electrodes with both ER and SP were found than would be expected based on chance ($p<.001$). This was also found when combining subjects ($p<.001$). For each subject a stimulation pair outside functional area, causing suppression in (part of) the SOZ, could be found. For one subject (female, 31 years), the ITC was determined for individual stimuli. No significant difference in ITC between the stimuli with suppression and the stimuli without suppression was found. A difference in the distribution between up and down phase was seen.

Conclusion: The occurrence of SP was strongly associated with the occurrence of ERs. However, response electrodes with SP are no perfect subset of response electrodes to whom an ER is evoked. Further research is needed to investigate whether cortical stimulation, suppressing power after SPES, is also effective in reducing epileptiform activity. In one subject we did not identify significance in phase coherence right before stimulation. Studying more subjects would be appropriate to reach a definite conclusion about the influence of the phase on the occurrence of power suppression after SPES.

List of Abbreviations

C	Regularization parameter (SVM)
ThL	Lower threshold (hysteresis)
ThU	Upper threshold (hysteresis)
AUC	Area under the curve
CCEP	Corticocortical evoked potential
CLE	Central lobe epilepsy
DBS	Deep brain stimulation
DHFS	Delayed high-frequency suppression
DR	Delayed response
ECoG	Electrocorticography
EEG	Electroencephalography
ER	Early response
ERSP	Event-related spectral perturbation
ESM	Electrical stimulation mapping
IED	Interictal epileptiform discharge
IEMU	Intensive epilepsy monitoring unit
ISI	Inter-stimulus interval
ITC	Inter trial coherence
LMCx	Lateral motor cortex
MMCx	Medial motor cortex
OR	Odds ratio
ppTMS	paired pulse transcranial magnetic stimulation
REC2Stim	Rational Extra-Eloquent Closed-loop Cortical Stimulation
SEEG	stereoelectroencephalography
SOZ	Seizure onset zone
SP	Suppressed power
SPES	Single Pulse Electrical Stimulation
SSEP	Somatosensory evoked potentials
SVM	Support vector machine
TF	Time-frequency
VNS	Vagal nerve stimulation

Contents

Chapter 1

Introduction

Central lobe epilepsy (CLE)

The prevalence of extratemporal epilepsy in patients with focal epilepsy is 55%, most often of frontal lobe or central (perirolandic) origin [1]. Central lobe epilepsy (CLE) originating from the pre- and/or post-central gyrus is often medically refractory with a high seizure frequency of daily seizures. Symptomatic seizures in the central lobe are convulsive and are known for their long duration, sometimes resulting in epilepsy partialis continua with uninterrupted twitches in a limb for days to years. These convulsive seizures are highly visible, which has a large impact on quality of life [2]. Since cognition is not impaired (at seizure onset), the patient himself is aware of the adverse effects of the seizure. This can result in fear. CLE patients usually undergo many drug trials and end up for diagnostic screening for epilepsy surgery. Even with visible lesions on the MRI or with clear lesions in or near eloquent cortex, surgery is not the evident choice. Invasive diagnostic methods may ensue in desperate cases, e.g. subdural electrode grid EEG recordings (electrocorticography, ECoG) for 7-10 days, in the small hope that the seizure onset might be just outside the functional central lobe. ECoG signals related to seizures are analysed to approximate the epileptogenic zone. The increased risk for postoperative neurologic deficits is higher than in other locations [3], as most of the central lobe is indispensable for sensorimotor function. Newly developed functional loss after CLE surgery was found in 54.4%, in the form of a sensory deficit, a motor deficit or both [4]. Only 31% of the CLE patients turned out seizure free (Engel class I) at follow-up [1].

Electrical stimulation

As CLE has a large impact on quality of life, it is important to find an alternative treatment that abolishes seizures without causing neurologic deficits [2]. Such an alternative treatment option for epilepsy may be electrical stimulation of the brain [5]. Stimulation treatment has been applied in different forms. Closed-loop or responsive stimulation and open-loop stimulation are two different approaches. In closed-loop stimulation, electrical pulses are delivered upon detection of electrographical epileptiform activity building up towards a clinical seizure. In open-loop stimulation, electrical pulses are delivered at a pre-programmed time, that does not change in response to neural activity. This can be either continuously or intermittently [6, 7]. Chronic intermittent, open-loop electrical stimulation, such as vagal nerve stimulation (VNS) and thalamic deep brain stimulation (DBS), usually target the whole brain. This type of stimulation does not require seizure localization or seizure detection. However, VNS studies show response rates between 40% and 50% and long-term seizure freedom in 5-10% of the patients only [8]. Stimulation applied to the epileptogenic focus only is called local or direct stimulation. Direct cortical stimulation has a higher seizure frequency reduction than DBS. Kinoshita et al. used 0.9 Hz electric cortical stimulation on the SOZ and non-epileptic areas to compare spike frequency before and after stimulation. The number of spikes at the electrodes in the SOZ significantly decreased as compared to the baseline ($p<.05$) after stimulation of the SOZ [9]. Yamamoto et al. also used low-frequency (0.9 Hz) electric cortical stimulation in patients with intractable partial epilepsy. They observed a decreased number of interictal epileptiform discharges [10, 11]. In addition, when stimulation was applied to the seizure onset zone the frequency of simple partial seizures in one patient decreased. These results suggest that low frequency electrical cortical stimulation has an inhibitory effect not only on the interictal but

also the ictal activities in patients with intractable partial epilepsy. However, as the SOZ is located in eloquent area for CLE patients, stimulation might cause symptoms [12].

REC2Stim

Recently, a new local stimulation therapy for CLE patients was proposed: Rational Extra-Eloquent Closed-loop Cortical Stimulation (REC2Stim). The REC2Stim clinical trial has yet to be started, but will recruit 10 patients with CLE. REC2Stim uses electrical stimulation within a local epileptogenic network, but outside the functional region to prevent undesired motor effects such as muscle contractions or interfere with sensorimotor performance. Elisevich et al. have stimulated outside the SOZ (near the epileptogenic zone) and observed a 90% decrease in interictal spike rates in the epileptogenic zone during electrical stimulation mapping (ESM) [13]. This supports the idea that stimulation outside the SOZ could be effective in suppressing interictal spikes. In REC2Stim, closed-loop cortical stimulation, delivering electrical pulses upon detection of electrographical epileptiform activity, will be applied to abort the build-up to a seizure. Participants of the REC2Stim trial undergoing clinical intracranial ECoG monitoring will prolong their clinical intracranial ECoG monitoring with two extra monitoring days. Systematic testing of different stimulation settings and their effect on interictal epileptiform EEG activity will be performed, to determine the optimal stimulation site and parameters. A location connected to the SOZ in the central lobe, but outside eloquent cortex is sought. Such sites are usually found, as the SOZ is often widely connected [14]. We aim to further characterize these sites and pick the most promising one(s) by looking at extra features from single pulse electrical stimulation (SPES).

Single pulse electrical stimulation (SPES)

In the University Medical Center Utrecht, SPES is part of the clinical routine during chronic electrocorticography. Single current pulses of 0.2 Hz are applied to adjacent electrode pairs on the grid. Different SPES responses can be observed, described as either a physiological response or a pathological response. The single pulses evoke an early response (ER), a physiological response, in an electrode elsewhere on the grid if the underlying regions are connected [15]. The ERs are seen within 100 ms after stimulation and are used to establish an effective functional connectivity network map. Functional connectivity is defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions [16]. Matsumoto et al. established functional connectivity between the lateral motor cortex (LMCx) and the medial motor cortex (MMCx) by applying single-pulse electrical stimuli. Short-latency cortico-cortical evoked potentials (CCEP), also referred to as ERs, were observed when stimulating MMCx and recording from LMCx and vice versa [17]. The second SPES response, pathological delayed responses (DR $>$ 100 ms), are associated with the seizure onset zone (SOZ) and are used to help identify the epileptogenic cortex [18, 19]. Both responses are shown in Figure 1.1. Time-frequency (TF) figures are computed to display the spectral changes after SPES, for example Figure 2.1.

Recently, attention has focussed on a new type of SPES response; a suppression of power in frequencies below 250 Hz [21, 22]. Davis et al. reported delayed high-frequency suppression (DHFS) elicited by SPES, as a significant feature to estimate the SOZ. Alarcon et al. analyzed activity of single neurons during IEDs and after SPES and identified similar behaviour. They hypothesized that SPES and IEDs trigger similar normal neurophysiological mechanisms, probably initiated by brief synchronized burst firing in some cells followed by long inhibition. We hypothesized that there are differences in connections between the cortex underneath the electrodes, causing a suppression picked up in one electrode while not by another. We expected to find a suppression in recording electrodes with an underlying connection to the stimulus pair. The exposure of underlying cortical connections (to the SOZ) is believed to help with choosing the optimal stimulation location for the suppression of epileptic discharges. Based on the results from Yamamoto et al. and Kinoshita et al., we hypothesized that power suppression after SPES spur

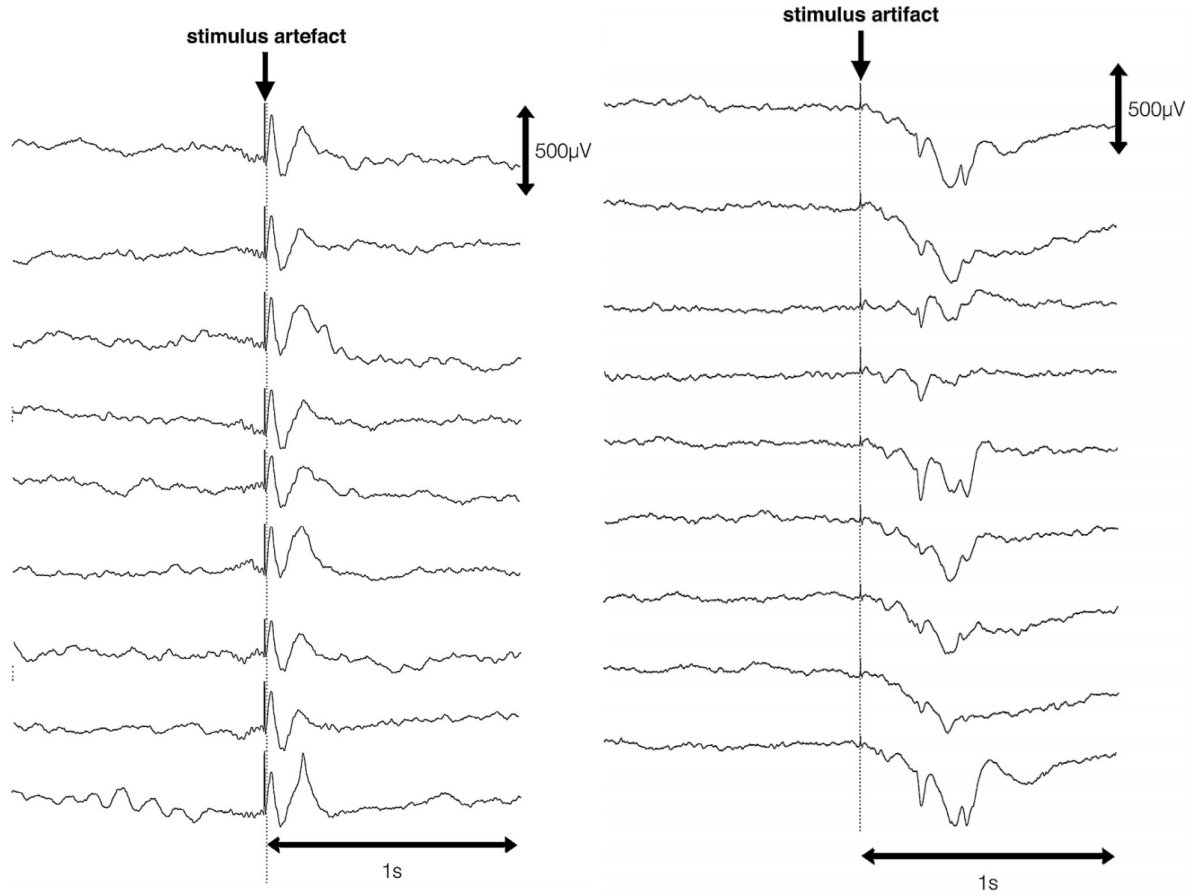


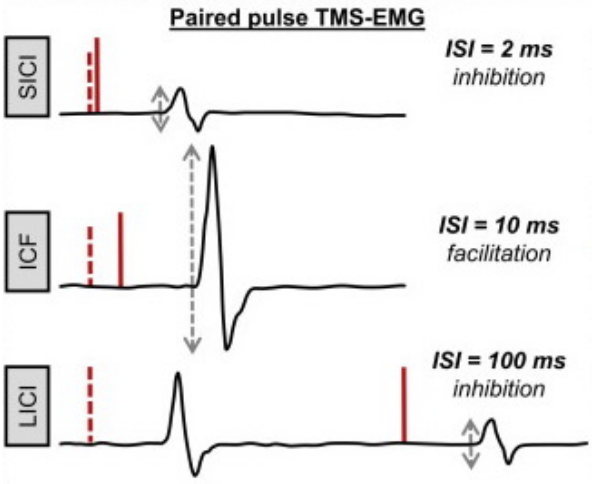
Figure 1.1: An example of a stereoelectroencephalography (SEEG) signal from the right temporal lateral cortex after SPES (0.2 Hz, 1 ms, 3 mA) by Boulogne et al. The stimulus artefact is seen as a vertical line. In the left figure, each line corresponds to the activity recorded in the posterior hippocampus after several identical amygdalar stimulations. ERs were observed after every stimulation, with a reproducible N1-N2 morphology and latency. These occur within 100 ms after stimulation. In the right figure, each line corresponds to the activity recorded in the orbito-frontal cortex after several identical temporal stimulations. DRs are seen on the right between 200 ms and 500 ms after stimulation. The DRs were not seen after every stimulation and could present variable latencies and shapes [20].

an inhibitory response that may enhance the anti-seizure effect of therapeutic stimulation, and could be indicative for the location of cortical network stimulation. Since for nearby stimulation suppression could also be a direct effect of the stimulus current, we wanted to make a distinction between adjacent and distant electrodes.

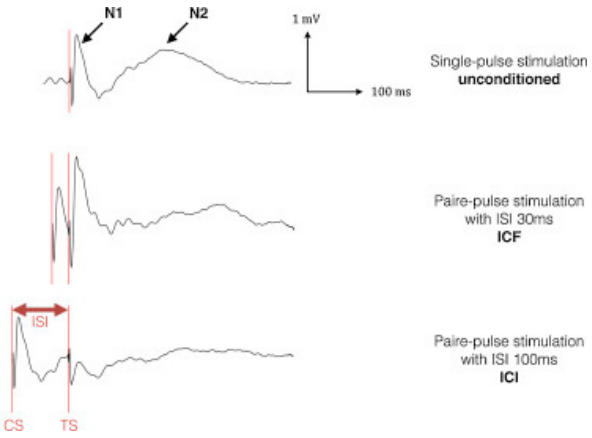
Phase

Besides the stimulation location, it has been suggested that the phase of the signal in the recording electrode at the moment of stimulation could have an impact on the response [20, 23, 24]. Shien Wei Ng et al. showed that stimulus selective firing patterns imprint on the phase rather than the amplitude of slow (theta band) oscillations in local field potentials and EEG. Another method in which the timing of stimulation could define the response is during paired pulse transcranial magnetic stimulation (ppTMS). It is a non-invasive method to examine cortical excitability [24, 25]. The ppTMS protcol contains a sub-

or suprathreshold conditioning stimulus followed by a suprathreshold test stimulus that elicits a motor evoked potential from the muscle. The time interval between the two stimuli, as well as the intensity of the conditioning stimulus, determine whether there will be a facilitatory or inhibitory influence on the test stimulus, see Figure 1.2a. Also, invasive EEG recordings have shown differences in single and paired-pulse electrical stimulation [20]. ERs were facilitated when an inter-stimulus interval (ISI) of 30 ms was used, while inhibited when the ISI was 100 ms (Figure 1.2b). We hypothesized that the first stimulus could reset the phase of the signal. A facilitatory or inhibitory influence is seen, depending on the phase change during the inter-stimulus interval. We made a link to the suppressions observed after SPES that have an inconsistent appearance. The timing at which the stimulations are applied, might relate to the phase of the ECoG and influence the elicited response. A suppression could therefore be influenced by difference in phase. It would be useful to explore whether the moment of stimulation is related to successful suppression, and therefore suppression of epileptic discharges after electrical stimulation could be related to the phase of the ECoG signal at the moment of stimulation. In this explorative study, we researched the power suppression after electrical stimulation. We did not aim to understand and model the phenomenon, but to assess its potential relevance for the REC2Stim study.



(a) Figure adjusted from de Goede et al. [26]. Outcome for ppTMS-EMG. Red straight lines = test stimulus, red dashed lines = conditioning stimulus. SICI = short intracortical inhibition, LICI = long intracortical inhibition.



(b) Figure adjusted from Boulogne et al. [20]. Early responses modulation induced by paired-pulse intracranial electrical stimulation. The SPES (0.2 Hz, 1 ms, 3 mA) elicited an ER. During paired pulse stimulation, a CS was associated with a TS. With ISI 30 ms, ICF was observed and with ISI 100 ms, intracortical inhibition (ICI) was observed.

Figure 1.2: Paired-pulse stimulation both non-invasive **(a)** and invasive **(b)**. ICF = intracortical facilitation and ISI = interstimulus interval. In both methods, a short ISI of 10 ms and 30 ms causes facilitation, while the ISI of 100 ms causes inhibition.

1.1 Research questions

The REC2Stim trial aims to effectively suppress chronic seizures in CLE patients. As the protocol for finding the ideal stimulation location still has to be established, part of this research focussed on investigating what stimulus-evoked signal characteristics may reduce the number of potential stimulation locations. We investigated whether an optimal stimulation location could be found for each of the included subjects. This led to the following research questions:

1. To what extent is it possible to explore the suppression phenomenon observed in TF images after applying SPES
   (a) Detection of suppression:
      i. How can we automate identification of SP?
   (b) Characteristics of the suppression:
      i. Can we characterize the suppression, e.g. with area, duration and frequency range, and are there factors influencing the inter-individual variability (e.g. location or connectivity)?
   (c) Relation between response electrode showing suppression and stimulus pair:
      i. Is there an association between the occurrence of a suppression in a response electrode and the underlying connection to the stimulus pair? i.e. is an ER a prerequisite for SP?
   (d) Is it possible for each subject to find a stimulation location, located outside functional area, that causes suppression in the SOZ electrodes after stimulation?
2. Does the phase of ECoG signals relate to the occurrence of suppression after stimulation?

Chapter 2

Power suppression detection - a machine learning approach

Contents

2.1 Objectives

The aim of this chapter was to develop an automated algorithm to detect the power suppressions in TF images in order to facilitate the analysis of the SP and the underlying neuronal network.

2.2 Methods

2.2.1 Subject characteristics

A machine learning algorithm was developed using ECoG data of four refractory epilepsy patients who underwent SPES between 2014 and 2018, two male/female, median 20 (range 10-34) years. The subjects were selected based on the location of the grid (a mixture of inside and outside the central lobe), and presence of suppressions after SPES (based on quick scanning of available SPES images). SPES was routinely performed as a clinical protocol. All patients were admitted to the intensive epilepsy monitoring unit (IEMU) of the UMC Utrecht in the Netherlands. Data were recorded at a sampling rate of 2048 Hz. Monophasic SPES stimuli with a duration of 1 ms, an intensity of 4-8 mA at a frequency of 0.2 Hz were given in each pair of adjacent electrodes, while the response was recorded from all other electrodes. Ten consecutive stimuli were applied to each stimulation pair, at a five second interstimulus interval. The SPES protocol as described by Valentin et al. was routinely performed [15, 27]. See Table 2.1 for the specification per subject.

2.2.2 Power suppression representation as ERSP

The neuronal responses to an electrical stimulation were observed in computed TF images. A representation in EEG lab using wavelet transforms was chosen. Event-related spectral perturbation (ERSP) was used to visualize event-related changes in spectral power over time in a broad frequency range [28]. The MATLAB® function *newtimef* was used to return the ERSP events across event-related trials of a single input time series. In each electrode, the average response to all ten stimuli of a stimulation pair were determined. To calculate the ERSP, the power spectrum over a sliding latency window was computed

Table 2.1: Study population. SPES code refers to the database number. The abbreviations for the different grid locations are: C=central, F = frontal, FB = frontobasal, HP = high parietal, IH = interhemspheric, P = parietal, T = temporal, aT = anterotemporal, subT = subtemporal.

Patient	Age/Sex	SPES code	Target	Grid Location	# Stimulus pairs/ electrodes	# TF images
A.1	34/F	119	SVM training	IH, P	48/56	2592
A.2	14/M	126	SVM training	C, HP	41/48	1886
A.3	10/M	130	SVM training	C, IH	29/40	1102
A.4	26/F	135	SVM testing	F, FB, aT, subT	39/56	2106

and then averaged across the ten data trials per stimulation pair. Wavelet cycles settings were set to [3 0.8], meaning the overlapping time window began with a 3-cycle wavelet. The number of cycles in the wavelets used for higher frequencies expanded slowly until 0.8 of the number of cycles was reached at the highest frequency. The time window was 1 s prior to and 1 s after stimulation. The mean baseline log power spectrum was subtracted from each spectral estimate to produce the baseline-normalized ERSP. The baseline was defined as [1 s - 100 ms] prior to the stimulation. Whether the deviation from the baseline power was significant, was assessed with the bootstrap method (significance level 5%). This means that a surrogate data distribution was constructed by selecting spectral estimates for each trial from randomly selected time windows in the baseline. These were averaged and was repeated several hundred times (default: N=200). A surrogate baseline amplitude distribution is produced, whose specified percentiles were then taken as significance thresholds. Output of the EEG lab function *newtimef* was the ERSP, for a series of time and frequencies, represented in a matrix and image. The minimal frequency was 10 Hz, determined by the number of data points, cycles and sampling frequency. An example of a TF image is shown in Figure 2.1. The number of TF images computed for each subject are shown in the last column of Table 2.1. These are the total number of responses, each representing a specific combination of a stimulus pair and a recording electrode.

2.2.3 Support vector machine (SVM)

Features

The TF images are used to detect and analyse the power suppressions of frequencies below 250 Hz after SPES [22], in the following referred to as suppressed power (SP). Automatic detection of SP in a TF image allows for rapid scoring of all stimulation pair-recording electrode combinations. The detection algorithm was developed with a support vector machine (SVM). The first step of the algorithm registered presence of blue samples in the TF image. Matlab's function *hysteresis* performs a dual thresholding operation on the ERSP matrix (in dB) using two threshold values (lower and upper). Values exceeding the upper threshold (ThU) were detected, creating a starting point. The lower threshold (ThL) was used to extend this starting point with the surrounding samples exceeding the lower threshold. The function created a matrix containing ones for the samples exceeding the thresholds, and zeros for the samples that did not. Two features were calculated from the matrix to detect a significant SP:

1. The total area of the suppressed power, using MATLAB® function *regionprops*. The area was defined as the sum of all joined samples passing the thresholds.

2. The duration (ms) of the suppressed power measured from start till end. The maximal duration was determined using equation 2.1.

$$duration = n_f * T_s, \tag{2.1}$$

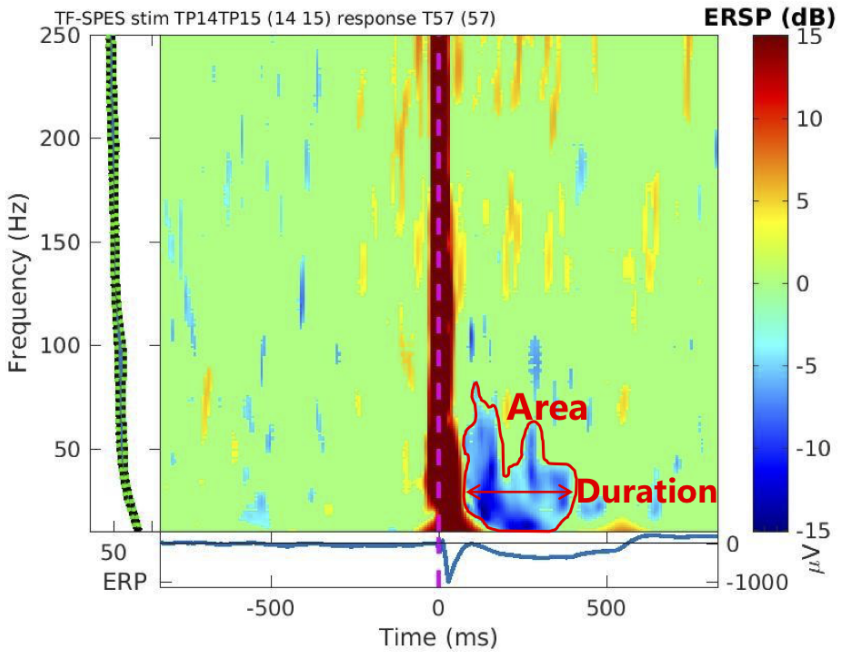


Figure 2.1: Example of a TF image of a recording electrode (T57) after stimulation by a stimulation pair (two electrodes: TP14 and TP15). Duration is described as the maximal horizontal distance. Area is defined as the total number of joined blue pixels of the suppression.

where n is the maximum number of samples at a certain frequency f and T_s the time resolution of the wavelet decomposition.

For the images in which multiple non-joined areas were detected, the surface with the largest size was selected. Both features were set to zero in the images in which no region was selected. The features were determined for all images in three subjects (A.1-A.3).

SVM construction

Three patients (A.1-A.3, a total of 5580 images) were used for training and validation of the SVM, see Table 2.1. These images were visually scored for the presence of an SP by two trained observers (MvdS/DvB). Interrater agreement was determined using Cohen's kappa [29]. The images that were disagreed upon were set to no SP, to reach a higher sensitivity. The MATLAB® function $fitcsvm$ with a gaussian kernel and cost function was implemented. A class dependent weight matrix ([0 1; 4 0]) was specified to incorporate a higher penalty on mistakes in the lower probability class. During training, the loss for the low probability class is multiplied with a weight that is inversely proportional to the fraction of the class of the total data [30]. The features 'area' and 'duration' were normalized to prevent the largest feature from dominating the prediction from the SVM according to the following equation:

$$x_j^* = \frac{x_j - \mu_j^*}{\sigma_j^*}, \tag{2.2}$$

where x_j is the feature, μ_j^* the weighted mean and σ_j^* the weighted standard deviation for observation j. A ten-fold crossvalidation was performed to optimize the hyperparameters: C, ThL and ThU. Parameters ThL and ThU were optimized, because different values lead to various area and duration sizes. C is the regularization parameter, which decides how much misclassification of each training example must be

avoided. A large values for C means less support vectors are being used. A small value for C means more support vectors and results in a larger-margin hyperplane, even if more training points are misclassified. All hyper parameters were optimized using grid search, with the following ranges: $C = 2^i$, with i=[-4:2:8]; ThL = [2:0.5:4]; ThU = [5:0.5:8]. The MATLAB® function *loss* was used to measure the trained SVM's predictive inaccuracy, and therefore the optimal hyperparameters. The final SVM model was trained on the entire training set, using the optimized hyperparameters. These upper and lower threshold and C value were consequently used for SP detection with the SVM [31, 30].

SVM performance

A new subject (A.4) was introduced to test the performance of the final SVM with the optimized hyperparameters. This was determined with performance measures; area under the curve (AUC), sensitivity and specificity.

2.3 Results

2.3.1 Support vector machine

SVM construction

Mean interrater agreement (MvdS/DvB) was 0.66 (SD 0.1). The highest performance was reached with the thresholds 5 dB (upper) and 4 dB (lower) for the MATLAB® *hysteresis* function and value 4 for parameter C. These parameters were found with a predictive inaccuracy (error) of 0.03.

SVM performance

An AUC of 0.88, specificity of 0.86 and sensitivity of 0.82 were acquired for the test subject (A.4).

2.4 Discussion

To train the SVM, two human observers scored the TF figures for the presence of a suppression as true labels. As SP was a newly observed phenomenon, a definition was not yet established. Consistent scoring of images on presence of SP was therefore difficult. This led to small blue spots to be scored as SP for the training subjects, while unintentional, this was not done for the test subject. Therefore, the trained SVM had a lower specificity (0.86) than possible. For future use of the SVM, re-scoring the train subjects could be useful to prevent detection of SP that are too small.

The features taken into account for the support vector machine were the area and duration of the suppression after the stimulation. The pre-stimulation period was not used for the SVM, but it was taken into account by the human observers. If a lot of spontaneous activity (excitation and suppression) was seen in the TF image in the pre-stimulation period, the suppression was not considered as an effect from the stimulation and therefore not scored as an SP. Another feature that was not considered by the SVM, but was unintentionally taken into account by the human observers was the timing of the suppression. The human observers were inclined to score a small suppression that appeared immediately after the stimulation and ignore a small suppression $>$ 500 ms after stimulation, as a suppression directly after stimulation is more likely to be caused by the stimulus. However, both Davis et al. and Maliia et al. reported delayed suppression. Davis described DHFS which were between 0.4-1 sec post-stimulation. Maliia observed inhibition 60-500 ms post-stimulation. Therefore, justification for scoring of early suppression rather than delayed suppression is debatable.

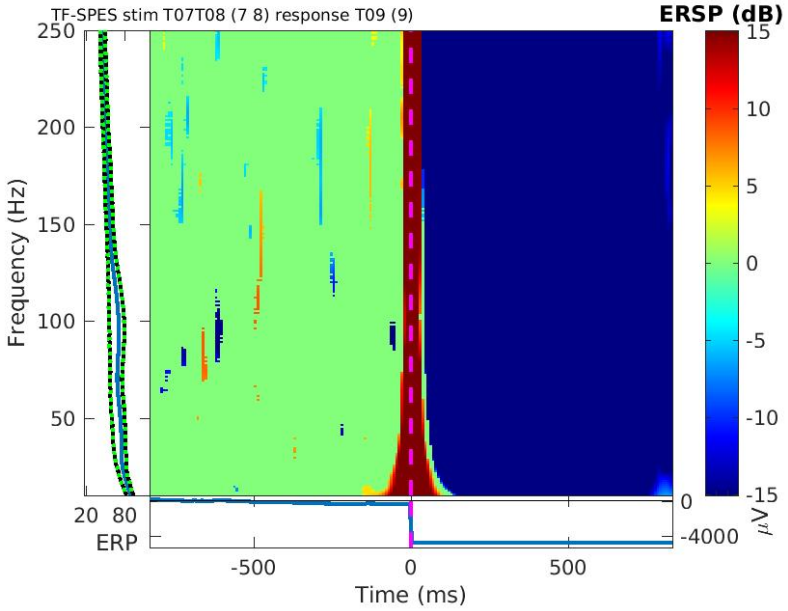


Figure 2.2: Example of a TF image of recording electrode T09 after stimulation by stimulation pair T07T08.

To improve the performance of the SVM, activity in the pre-stimulation period could be taken into account as well. Furthermore, the SVM was not trained well for recognizing artefacts. For example, saturation in the electrode next to the stimulation pair was not seen as an artefact but a 'legitimate' SP, see Figure 2.2. Stimulation in stimulus pair T07T08 caused saturation in the adjacent electrode T09. The post-stimulus period is considered as unreliable and needs to be removed from the analysis. Currently, these cases still need to be removed manually after visual inspection. For future improvement a new feature might be added to the SVM: the total number of samples with suppression in the post stimulus period. A large artefact due to e.g. current leakage from the stimulus pair could be detected. These adjustments could slightly improve the specificity of the SVM.

The performance of the SVM was determined in one test subject only (2106 images). Although the number of images are high, the performance could be different if multiple subjects were included. Still, the characteristics of the SP (e.g. area and duration) are not subject specific. Therefore, a similar performance is expected if the number of test subjects is increased.

2.5 Conclusion

An SVM facilitates the detection of power suppression using area and duration as features. Automatic detection is possible, but still requires visual inspection for false positives.

Chapter 3

Power suppression and the underlying network

Contents

3.1 Objectives

In this chapter we explored whether suppressed power (SP) was associated with the occurrence of an ER elicited by the same stimulation pair, and therefore, the presence of an effective connection between the stimulus pair and response electrodes. Features of the SP were determined - duration, area and frequency lower/upper limit - and analysed for different situations (presence of an ER and distance to the stimulus pair). Also the possibility to find a stimulation location outside eloquent cortex causing an SP and an ER in the SOZ response electrodes was explored.

3.2 Methods

3.2.1 Subject characteristics

A retrospective study using ECoG data of fourteen refractory epilepsy patients who underwent SPES between 2014 and 2018 was executed. Four subjects (A.1-A.4) had been used for the development of the detection algorithm with a SVM (Chapter 2). Here, ten other subjects (B.1 - B.10) were included for the SP analysis, six male and four female, median age 15, range 9-41 years. Six subjects had (one of) their grids implanted in the central lobe. The other four subjects had grids implanted elsewhere. SPES was routinely performed as a clinical protocol. All patients were admitted to the intensive epilepsy monitoring unit (IEMU) of the UMC Utrecht in the Netherlands. Data were recorded at a sampling rate of 2048 Hz. Monophasic SPES stimuli with a duration of 1 ms, an intensity of 4-8 mA at a frequency of 0.2 Hz were given in each pair of adjacent electrodes, while the response was recorded from all other electrodes. Ten consecutive stimuli were applied to each stimulation pair, at a five second interstimulus interval. In each subject, SP was observed during scanning of the SPES data. See Table 3.1 for the specification per subject.

Table 3.1: Study population. SPES code refers to the database number. The abbreviations for the different grid locations are: C=central, F = frontal, FB = frontobasal, HF = high frontal, HP = high parietal, IH = interhemspheric, Oc = occipital, P = parietal, T = temporal, aT = anterotemporal. # = number

Patient	Age/Sex	SPES code	Grid Location	# Stimulus pairs/ electrodes	# TF images
B.1	14/M	54	Oc, P, T	45/64	2790
B.2	15/F	78	C, F	55/64	3410
B.3	9/F	88	C, F, IH, T	70/80	5460
B.4	13/M	97	C, IH, P	48/56	2592
B.5	41/F	99	T, subT	44/64	2728
B.6	14/M	114	F, HF	42/48	1932
B.7	34/M	115	subT, TP, aT	69/96	6486
B.8	22/M	120	C, T	42/48	1932
B.9	18/F	123	C	53/64	3286
B.10	14/M	137	C	54/64	3472

3.2.2 Power suppression and early response

Association between SP and ERs

The trained SVM algorithm scored the TF images of ten subjects (B.1-B.10) on presence of an SP. The SVM's positive scores were visually checked by a human observer for false positives. ERs were determined with an automatic detector within 9-100 ms post stimulus. The detected ERs were visually checked (DvB) [14]. The ECoG signal in the stimulation electrode pair becomes saturated after each electrical stimulus during SPES. Therefore, these electrodes are discarded as response electrodes during the 50 s that they are used as stimulation pair, as we cannot obtain any information from the ECoG signal. If both grid and depth electrodes were implanted, the depth electrodes were left out in the analysis step. These will not be used in the REC2Stim trial and are therefore irrelevant for this study.

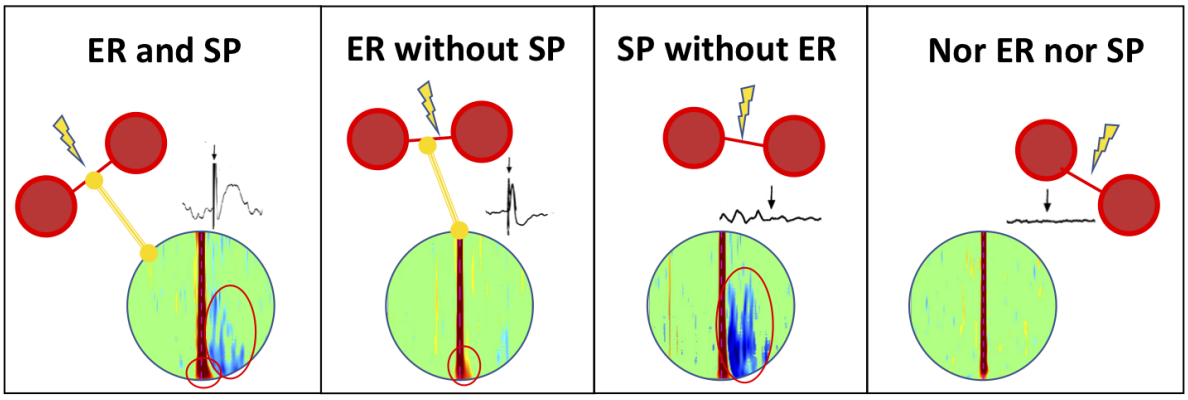


Figure 3.1: A visual representation of the different responses in a response electrode after stimulation of a stimulus pair. The yellow line represents a connection between stimulus pair and response electrode, i.e. an ER is present. The response electrode shows the response after SPES in the time-frequency domain. The SP is the blue spot in the TF image.

For each subject the number of response electrodes in which both ER and SP, either ER or SP, and

neither ER or SP were evoked by the same stimulus pair was determined. A visual representation of the four categories is shown in Figure 3.1. These numbers were also combined over all ten subjects. A chi-squared test was used to determine whether an SP was associated with the occurence of an ER. Also odds ratios (OR) as a measure of the association between an ER and an SP were determined [32].

SP features

Several features of the SP - duration, area and frequency lower/upper limit - were determined. Area and duration were established as described in chapter 2. The frequency lower/upper limit was set to the lowest and highest frequency value of the detected SP respectively. These features were distinguished according to presence of an ER and compared in boxplots.

Additionally, features of the SP adjacent to the stimulation pair, were compared to those that were located more distantly. An electrode was defined 'adjacent to a stimulation pair' if the electrode bordered one of the stimulation electrodes, see Figure 3.2. Since for nearby stimulation suppression could also be a direct effect of leakage of the stimulus current, we tested whether these features were significantly different in both groups with the Mann-Whitney U test. We assumed that if this effect is present, it is limited to directly bordering electrodes only. The test was performed for all ten subjects combined, as well as individually.

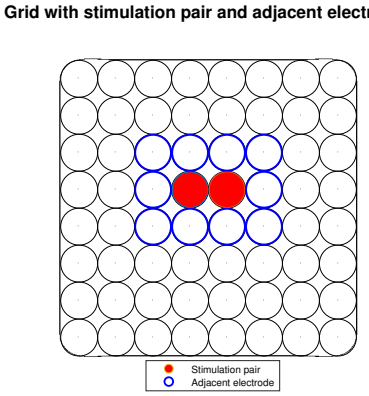


Figure 3.2: An example of a grid for one subject, with an arbitrarily chosen stimulation pair (red coloured). All blue outlined electrodes are defined as 'adjacent to stimulation pair'.

Distribution of location of SP and ERs

A schematic view of the grid with markers for electrodes with ERs, SP and the corresponding stimulation pair was constructed in order to assess the distribution of ERs and SP. Also, their location relative to the stimulus pair was analysed to get a sense of how the power suppressions are distributed over the brain.

3.2.3 Optimal stimulation pair

For each subject, it was investigated if a stimulation pair could be found outside functional area, causing suppression and ERs in (part of) the SOZ. An SP and an ER, implying a direct underlying cortical connection, had to be caused by the same stimulus pair-SOZ electrode combination. The SOZ is defined as the electrodes with the earliest ictal activity, as determined by an epileptologist (FL). Different intracranial electroencephalographic seizure onset patterns are associated with different epileptogenic lesions [33]. The functional or eloquent region was localized by means of direct ESM. During ESM, cortical stimulation (30-60 Hz) for 1-7 s is applied to small areas of cortex to observe its effect on

function [34]; e.g. an involuntary contraction of the thumb or other motor behaviour, an inability to name objects, or a tingling sensation in a finger. If stimulation in an electrode caused events like these, in combination with at least two other electrodes, the electrode was defined as functional electrode. Table 3.2 presents the SOZ and functional electrodes as well as the different seizure onset types for each individual subject. For every subject, all seizures were incorporated in the specifications in the table. Seizure clusters were excluded due to their complex nature. Degree of suppression was defined as the percentage of the SOZ electrodes in which an SP occurred. We speculate that the stimulation pair with the highest degree of suppression could be the ideal location for suppression of epileptic seizures without adverse effects in the REC2Stim study.

Table 3.2: Defined SOZ and functional electrodes per subject. The electrodes coloured in red are in the SOZ and functional area. The abbreviations for the different grid locations are: C=central, F = frontal, HF = high frontal, HP = high parietal, IH = interhemspheric, sOc = suboccipital, P = parietal, T = temporal, aT = anterotemporal. The red coloured electrodes are both SOZ and functional electrodes.

Patient	SOZ electrodes	Functional electrodes	Seizure onset type
B.1	sTa3-5, sTv5-7, sOc5, aT28	aT2,3,9-11,13,17-21,26,28	Gamma
B.2	FH21,22,27-30*,FL3-6,12,13,22	FH8,15,22,23,31, FL7,8,12,13,19,20,28	Beta/gamma
B.3	F1-4,9-12,17-20,25-28, IH2-7	F28, T36-40,43,44,46-48,55,56,63	Beta/gamma
B.4	C1,2,9,10,17-19,20, IHH9,10,11-13, IHL1,2	C1,2,3,9,10,17-19, IHH4,5,11-13	Spike and wave superimposed with gamma
B.5	T19,20,22,23,27-29	T11,18,22	Poly spike and wave discharges, gamma/beta
B.6	F3,4, HF10,11,15**	F8,15,16,19,22,24	Spike and wave complexes, followed by rhythmic beta and gamma
B.7	TP31,32,37-39	TP29	Beta
B.8	C4,5,12,13,14,20,21,22,27,28	T6,7, C5-8,10,11,13-15,17-20,21	Spike rhythm followed by gamma
B.9	C5,6,13,14,21,22,29,30,43-45	C4-6,12,13,14,21,22,35,36,43-45, 51-54,60-62	Beta
B.10	C13,14,20-22,28,29,30	C12,13,14,20-22,29,30,39,40,48,55,56	Spike and wave sequence, Gamma

* The grid did not cover the actual SOZ, as the SOZ was located in the deeper structures of the brain which were not sampled with electrodes. The selected SOZ electrodes show a diffuse spread pattern of the seizure.
** Depth electrodes contained part of the SOZ as well, but were not taken into account.

3.3 Results

3.3.1 Subject characteristics

Mean number of implanted electrodes was 68. Median number of TF images per patient was 3038 (range 1932 - 6486). An overview of the study population is shown in Table 3.1.

3.3.2 Power suppression vs Early response

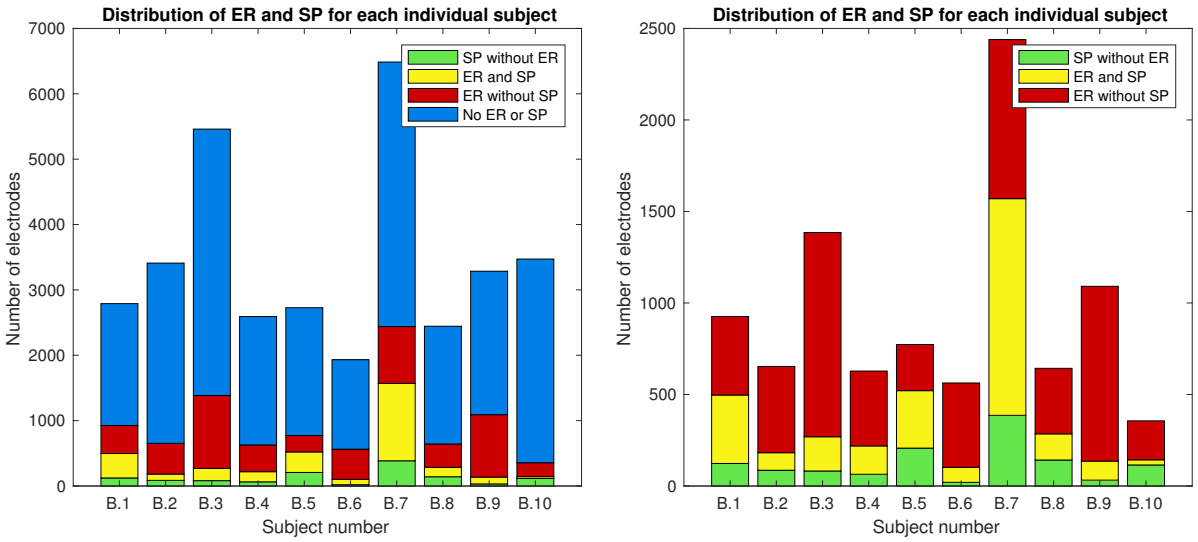
Association between SP and ERs

In all subjects, the percentage of SPES responses with SP was smaller than those with ERs. Averaged over ten patients; 11% of the responses contained an SP, while 24% of the responses had an ER. Subdivided in the four different categories averaged over ten subjects: 8% of the electrodes had an ER and SP, 16% an ER without SP, 3% an SP without ER and 73% no ER or SP. Of all stimulus pair - recording electrode combinations containing an SP, 68% had an ER as well. The details on each subject are shown in Table 3.3. Figure 3.3 shows in which numbers the four possible combinations of responses after stimulation occurred: no response, an ER, an SP, or both. Most common was absence of any response, seen in Figure 3.3a. Figure 3.3b focusses on the other three categories. ERs without SP were observed most. Furthermore, in nine out of ten subjects, the number of SP with ER was higher than the number of SP without ER. In each subject, significantly more responses with both ER and SP were found than would be expected based on chance ($p<.001$). A similar result was obtained when combining all ten

subjects (p<.001). The OR measuring the association between SP and ERs varied between 3.5 (subject B.10) and 14.3 (subject B.7), with a median of 10. An OR of 9.6 was reached when all subjects were combined.

Table 3.3: Results of the analysis on the association between ERs and SP are shown in this table. The amount of ERs and SP are presented as an absolute number, as well as a percentage of the total responses recorded for each subject between brackets. ORs and p-values for the chi-squared test for each subject individually and for all subjects combined are displayed.

Patient	#ER	#SP	#ER and SP	#ER without SP	#SP without ER	# No ER or SP	OR	p-value (chi^2)
B.1	803 (29%)	497 (18%)	374 (13%)	429 (15%)	123 (5%)	1864 (67%)	13.2	< .001
B.2	567 (17%)	182 (5%)	96 (3%)	471 (14%)	86 (2%)	2757 (75%)	6.5	< .001
B.3	1303 (24%)	269 (5%)	187 (3%)	1116 (20%)	82 (2%)	4075 (75%)	8.4	< .001
B.4	564 (23%)	219 (7%)	155 (6%)	409 (16%)	64 (2%)	1964 (76%)	11.6	< .001
B.5	566 (23%)	521 (19%)	314 (11%)	252 (9%)	207 (8%)	1955 (72%)	11.8	< .001
B.6	543 (21%)	102 (4%)	82 (4%)	461 (24%)	20 (1%)	1369 (71%)	12.2	< .001
B.7	2053 (28%)	1570 (24%)	1184 (18%)	869 (14%)	386 (6%)	4047 (62%)	14.3	< .001
B.8	501 (32%)	285 (12%)	143 (6%)	358 (14%)	142 (6%)	1801 (74%)	5.1	< .001
B.9	1059 (21%)	136 (4%)	104 (3%)	955 (29%)	32 (1%)	2195 (67%)	7.5	< .001
B.10	241 (7%)	143 (4%)	28 (1%)	213 (6%)	115 (3%)	3116 (90%)	3.5	< .001
All	**8200 (24%)**	**3924 (11%)**	**2667 (8%)**	**5533 (16%)**	**1257 (3%)**	**25143 (73%)**	**9.6**	**< .001**



(a) (b)

Figure 3.3: **(a)** A response electrode - when stimulated by a specific stimulation pair - can show four combinations of possible responses; neither SP nor ER, ER without SP, SP without ER, or both ER and SP. **(b)** Zooms in on the low prevalence classes.

SP features

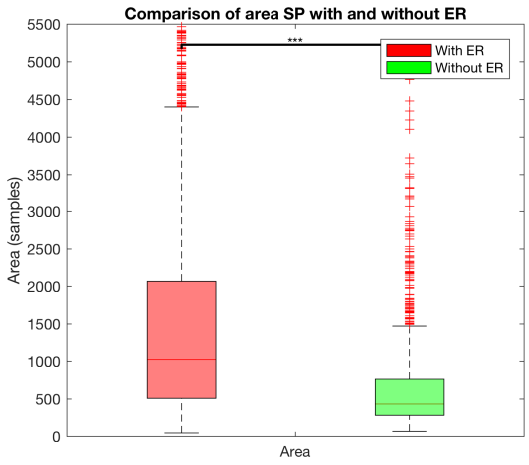
With/without ER

The SP features - area, duration and the lower limit and higher limit of the frequency rang - in the electrodes in which both ER and SP occurred, were compared to the features of the electrodes with an SP only (see Figure 3.4). At group level, the area of SP was higher when an ER was present than when an ER was absent (respectively 1023 samples and 431 samples, p<.001), Figure 3.4a. In eight subjects (B.1-B.7, B.9), the results were similar. For subjects B.8/B.10 this did not hold statistically (p>.05), Figure 3.5a. The duration of SP was higher when an ER was present than when an ER was

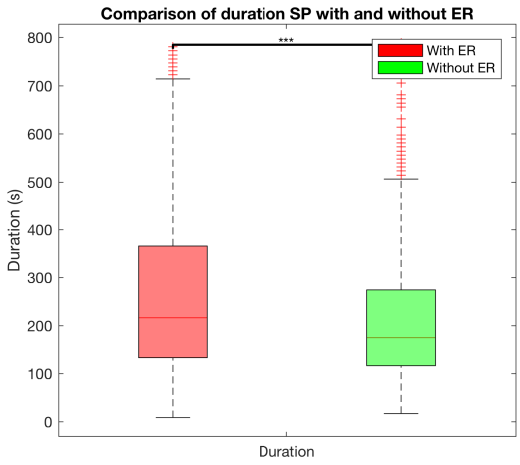
absent (respectively 216 ms and 174 ms, p<.001). Conflicting results were found at the individual level. For four subjects the same result was found (p<.001). In one subject the opposite result was found (p<.001). For the remaining five subjects (four CLE patients) the difference did not hold statistically (p>.05), see Figure 3.5b. Furthermore, for all subjects combined the median lower limit frequency was 10 Hz with and without an ER. Still, with ER an overall higher lower limit was found (p<.001). For three subjects the same result was found (B.2,B.4,B.9). The upper limit of the frequency range was higher when an ER was present than when an ER was absent (respectively 89 Hz and 49 Hz, p<.001), Figure 3.4d. The same result was obtained for eight individual subjects (B.1-B.7, B.9).

Adjacent/non-adjacent

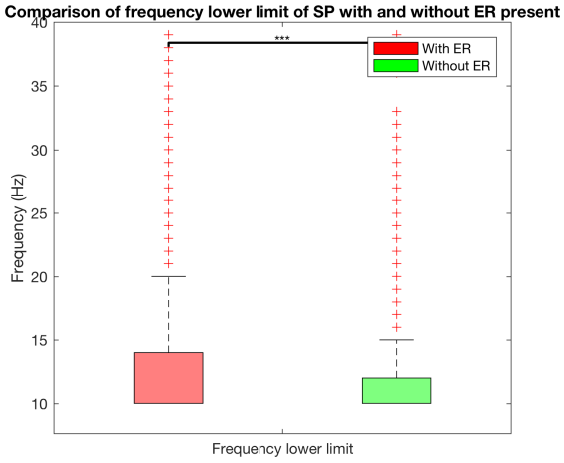
The SP features in the electrodes adjacent to the stimulus pair were compared to the features in the electrodes distant to the stimulus pair (Figure 3.6). The SP area was lower in adjacent electrodes than distant electrodes (respectively 74 samples and 92 samples, p<.001). This holds statistically for two individual subjects (B.1, p=.008 and B.2, p=.005), see Figure 3.7. The other eight subjects had a p value $>$ .05. Also the duration of the SP in adjacent electrodes was lower than distant electrodes (25 ms and 33 ms respectively, p<.001). In subject B.1 and B.2 the same result was found (p=.02) and (p=.002). The other eight subjects had no significant difference on an individual level. Furthermore, on group level the median lower limit frequency of the SP is 10 Hz for both groups. Still, for the distant electrodes an overall higher frequency lower limit was found (p = .002). The upper limit of the frequency range of the SP in the electrodes adjacent to the stimulus pair was lower than when the electrodes were distant to the stimulus pair (33 Hz and 36 Hz respectively, p<.001). The same result was obtained for two individual subjects (B.1, p=.03 and B.2, p=.02). The other eight subjects had no significant difference on individual basis.



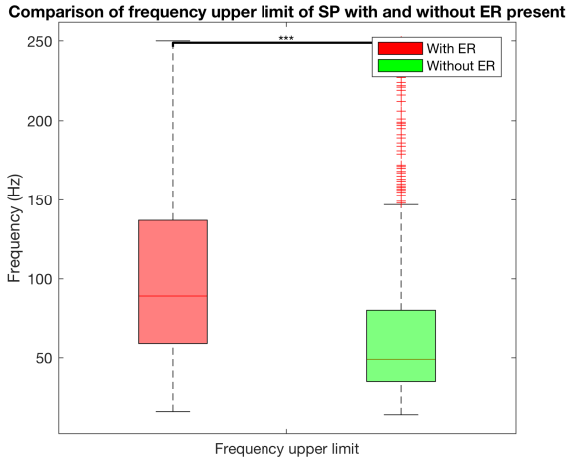
(a) Area of the SP in samples.



(b) Duration of the SP in seconds.

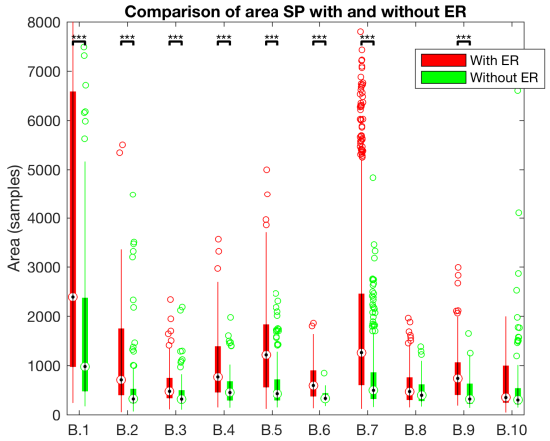


(c) Lower limit of the SP's frequency range

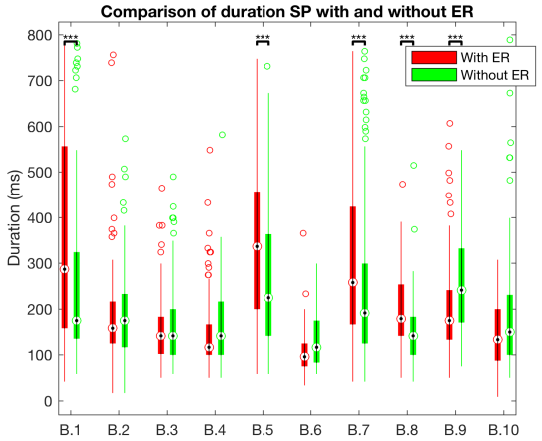


(d) Upper limit of the SP's frequency range

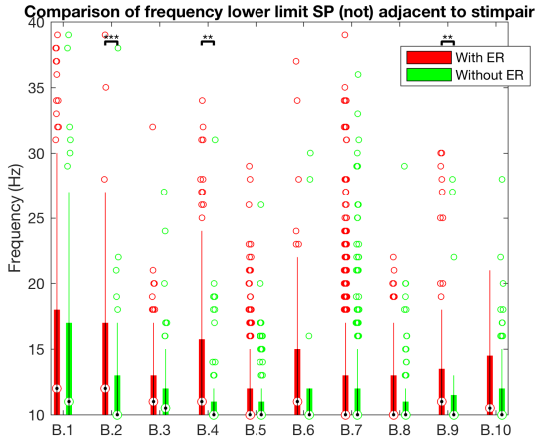
Figure 3.4: Boxplots showing different features of the SP when an ER is or is not present for all subjects combined. On each box, the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers, and the outliers were plotted individually using the '+' symbol. $*$:p$<$.05, $**$:p$<$.01, $***$:p$<$.001.



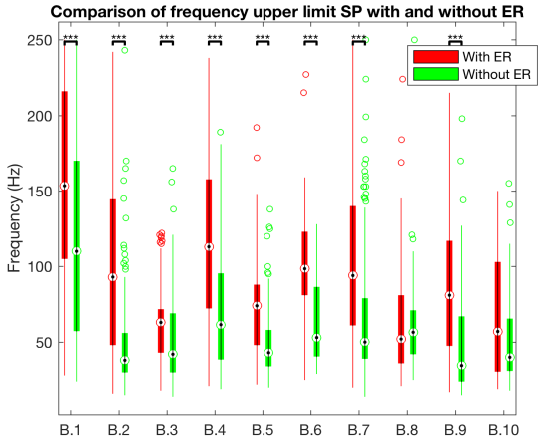
(a) Area of the SP in samples.



(b) Duration of the SP in seconds.

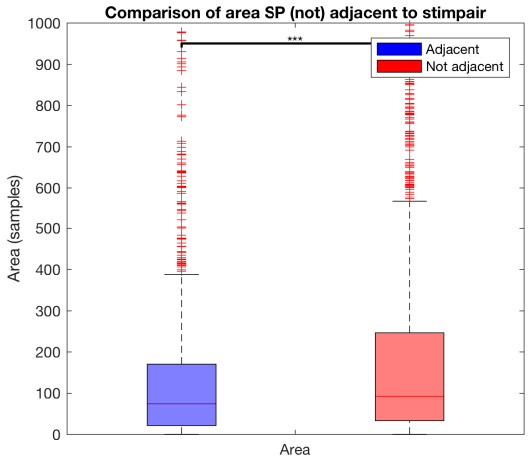


(c) Lower limit of the SP's frequency range

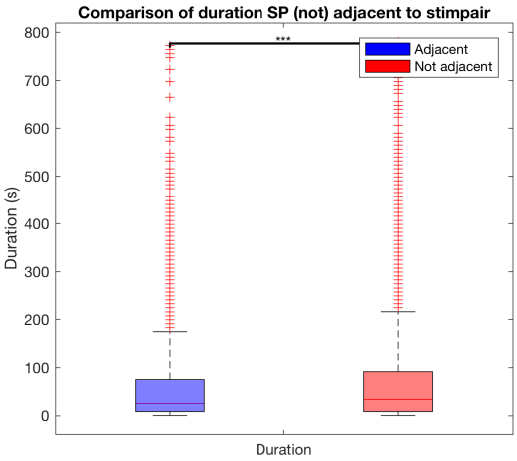


(d) Upper limit of the SP's frequency range

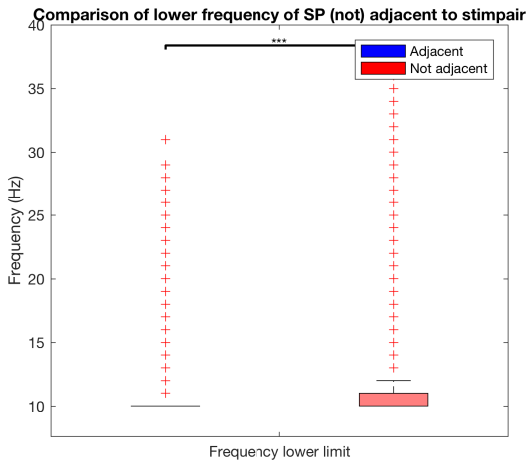
Figure 3.5: Boxplots showing different features of the SP when an ER is or is not present for all subjects individually. $*$:$p<.05$, $**$:$p<.01$, $***$:$p<.001$.



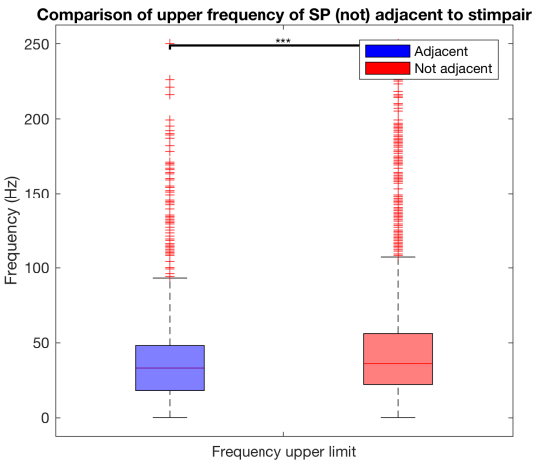
(a) Area of the SP in samples.



(b) Duration of the SP in seconds.

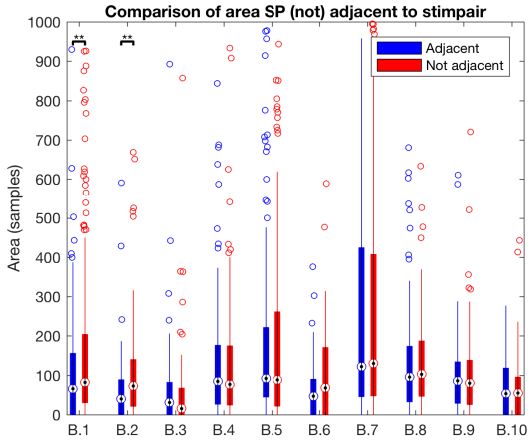


(c) Lower limit of the SP's frequency range

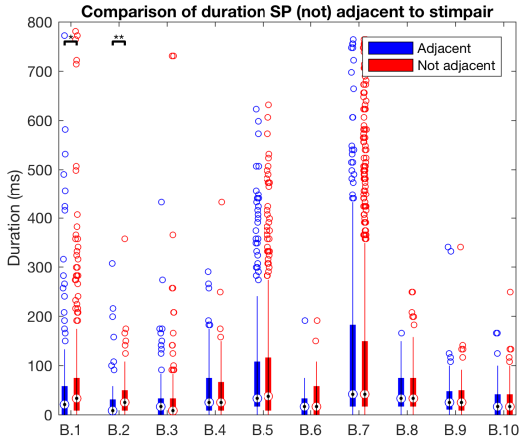


(d) Upper limit of the SP's frequency range

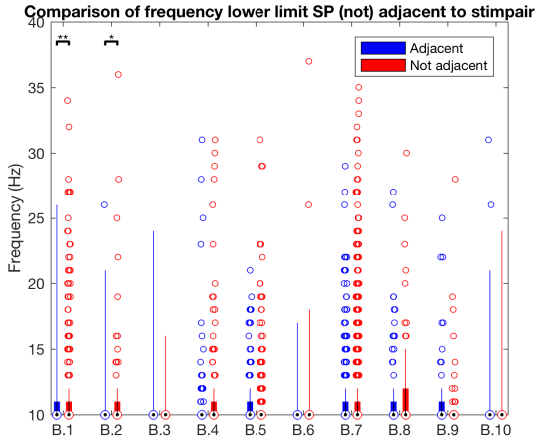
Figure 3.6: Boxplots showing different features of the SP for the electrodes with an SP which are (not) adjacent to the stimulus pair for all subjects combined. On each box, the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers, and the outliers were plotted individually using the '+' symbol. $*$:$p<.05$, $**$:$p<.01$, $***$:$p<.001$.



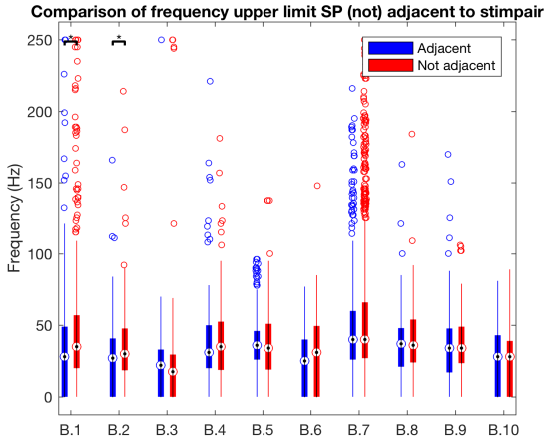
(a) Area of the SP in samples.



(b) Duration of the SP in seconds.



(c) Lower limit of the SP's frequency range

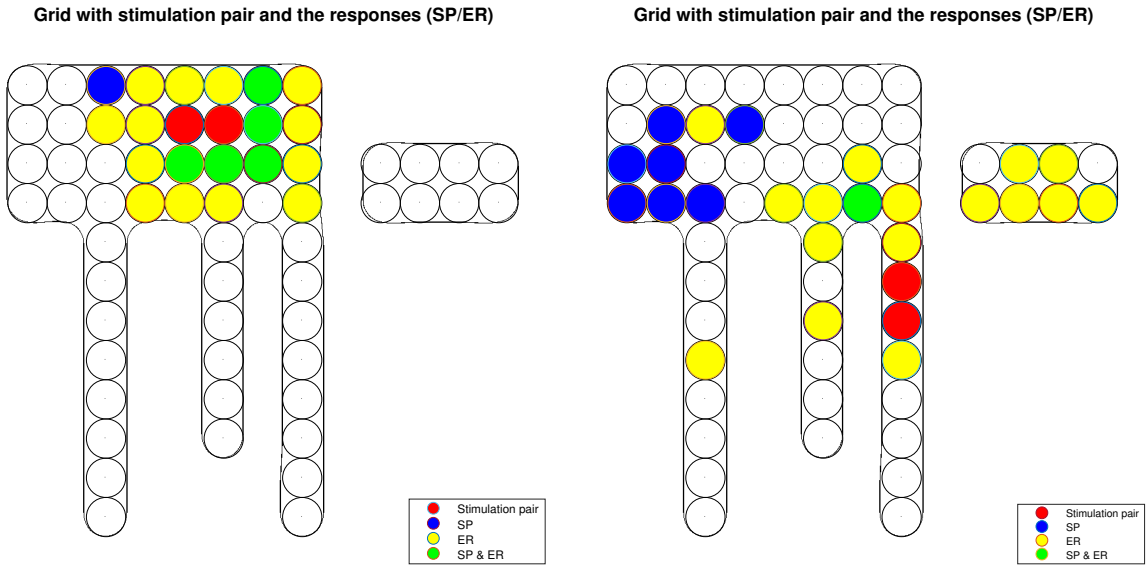


(d) Upper limit of the SP's frequency range

Figure 3.7: Boxplots showing different features of the SP for the electrodes with an SP which are (not) adjacent to the stimulus pair for all subjects individually. $*$:p$<$.05, $**$:p$<$.01, $***$:p$<$.001.

Location distribution of SP and ERs

In general, both ERs and SP were observed in great numbers around the stimulus pair (Figure 3.8a). However, the location of the SP after stimulation is not restricted to this area (Figure 3.8b). Power suppressions occur in both electrodes with and without an ER.



(a) (b)

Figure 3.8: Both grids are from subject 1. The grids show the responses and its locations after stimulation in a different stimulation pair. **(a)** Most responses surround the stimulation pair. **(b)** Responses can also occur more distantly from the stimulation pair.

3.3.3 Optimal stimulation pair

The optimal stimulation pair for each subject is presented in Table 3.4. In subject 1 and 5 the number of SOZ electrodes showing SP was the highest, reaching 88% and 86% of the SOZ electrodes respectively. Subject 9 had the least amount of SP (9% of the SOZ electrodes).

Table 3.4: For each subject the optimal stimulation pair causing suppression in the SOZ. The amount of suppression is presented in a percentage, with the absolute number of electrodes.

Patient	Optimal stimulation pair	Suppression (percentage)
B.1	aT30-31	88% (7/8)
B.2	FH19-20	23% (3/13)
B.3	F29-30	27% (6/22)
B.4	C25-26	33% (5/15)
B.5	T30-31	86% (6/7)
B.6	F17-18	40% (2/5)
B.7	TP26-27	60% (3/5)
B.8	C23-24	60% (6/10)
B.9	C26-27	9% (1/11)
B.10	C18-19	13% (1/8)

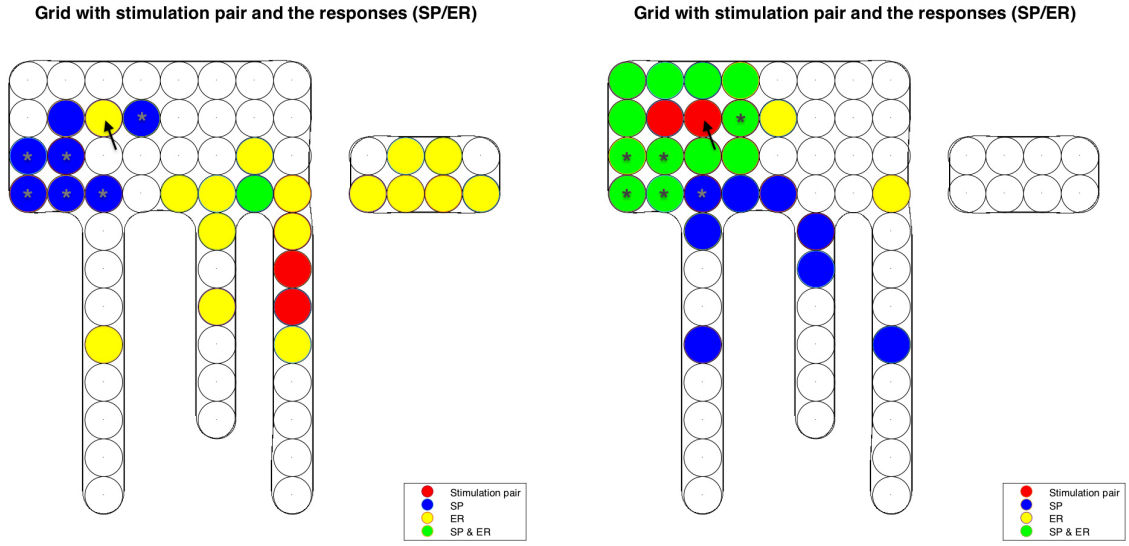
3.4 Discussion

We explored whether power suppression after SPES was associated with the occurrence of ERs. As we hypothesized that power suppression after SPES might serve as a surrogate marker for inhibition of epileptiform activity, we used the presence of SP after SPES, after stimulation outside eloquent cortex, to find the optimal stimulation location for the REC2Stim trial.

3.4.1 Interpretation results

SP vs ERs

The overall number of ERs is higher than the number of power suppressions for each subject, Figure 3.3. It means that an ER is not necessarily followed by an SP and thus not a general feature of effective connectivity. For nine out of ten subjects (B.1-B.9), the number of SP with ER was higher than the number of SP without ER. The opposite was found in subject B.10. This subject had ERs to 7% of all stimulations, compared to a mean of 24% (std 5%) in the other subjects (Table 3.3). Multiple periods of sub clinical seizures and interictal spikes were observed during the SPES session, which may explain the small number of ERs. It is commonly assumed that interictal spikes set off a period of inhibition that transiently reduces tissue excitability [35]. For all ten subjects, a chi-squared test showed that the occurrence of SP was strongly associated with the occurrence of ERs. Also ORs > 1 were found for each subject (Table 3.3). The fact that an electrode with an ER has a higher chance of an SP than an electrode without an ER, implies that the SP exists mainly when the cortical tissue underneath the stimulus pair and recording electrode are connected. However, power suppressions without an ER can also occur, meaning that the electrodes with an SP are not a subset of the electrodes with ERs.



(a) (b)

Figure 3.9: Subject B.1. Distribution of the responses (ER/SP) after stimulation in different stimulation pairs (red electrodes). **(a)** The stimulation pair causes suppression in multiple electrodes located at a distance from the stimulation pair. The stimulus electrodes are connected with the electrode with the black arrow (ER present). The electrodes with a star correspond with electrodes in which the stimulus pair from (b) also causes a suppression. **(b)** The (stimulus) electrode with a black arrow is connected to the stimulus pair from (a). The stimulus pair in this figure causes suppression and has a connection with electrodes that the stimulus pair from (a) also causes suppression in (see electrodes with star).

The schematic grids displaying the locations of SP and ER (Figure 3.9a), show SP without ERs in electrodes far away from the stimulation pair. This suggests that there is no direct connection between the cortical tissue underneath the stimulus pair and the electrode showing the SP. A second order connection could explain this. If the stimulation pair in Figure 3.9a is stimulated, the SP in electrodes without an ER could be caused by the connection electrode indicated with a black arrow, since stimulation in that electrodes shows SP in the same recording electrodes (electrodes indicated with a star, Figure 3.9b). The order number of connections to pass on the suppression could be variable.

SP features

With/without ER

SPs were characterized by 4 features: area, duration and frequency lower and upper limit. Three features were enhanced when an ER was present (area, duration and frequency upper limit). This suggests that a direct underlying connection, implied by the ER, could lead to a more prominent suppression. If there is no direct connection and the suppression is possibly caused by a second order connection, the suppression is more restricted in its area, frequency range and duration. The fourth feature, frequency upper limit, had a median of 10 Hz with and without an ER which was also the minimum value in both groups. Based on an elevated frequency upper limit with an ER, we would expect a lower frequency lower limit for an SP with an ER. As the minimum frequency value was restricted to 10 Hz by the settings of the wavelet transform, it is not possible to use this feature to distinguish between the two groups.

Adjacent/non-adjacent

For most individual subjects (B.3-B.10), there was no difference in SP features between adjacent and distant stimulation. At group level, the area was found larger in an electrode more distant to the stimulus pair ($p<.001$), with longer duration ($p<.001$), higher frequency upper limit ($p<.001$) and higher frequency lower limit ($p=.002$), Figure 3.6). This implies that the suppressions are not an artefact due to current leakage from the stimulation pair to the surrounding electrodes.

Optimal stimulation pair

Two subjects (B.1 and B.5) had an SP in more than 80% of the SOZ electrodes, with the selected optimal stimulation pair. These subjects have in common that the SOZ is located in the temporal lobe. Four of the subjects (B.2, B.3, B.9 and B.10) had a suppression in less than 30% of the SOZ electrodes. Subjects 2 and 3 were sleeping during (part of) the SPES session. Usami et al. observed a stronger cortical connectivity (N1 size) and excitability (high-gamma activities) after SPES during sleep, depending on sleep stage. They do not report an increase or decrease in number of CCEPs [36]. Subject B.10 had more than 200 seizures during the entire intracranial recording. Also during the SPES session, multiple seizures occurred. This could have influenced the responses. All four subjects with a suppression in less than 30% of the SOZ had a relative low number of suppressions (see Table 3.3). Subjects 2 and 3 had an SP in 5% of all responses, and subjects B.9 and B.10 in 4% of all responses. The other subjects had an average of 16%. This lower number of suppression reflects that it is more difficult to find a stimulation pair causing suppression in a high percentage of SOZ electrodes.

3.4.2 Methodological aspects

TF figures

The minimal lower limit of the frequency range in the TF figures was 10 Hz, which was defined by the number of data points, cycles and sampling frequency. A minimum of 10 Hz means that the lowest physiological frequency band to be distinguished is the beta and (part of) alpha band. Rapid discharges (EEG high-beta or low-gamma band) are frequently observed during the transition from interictal to

ictal activity [37]. As this will be the moment of stimulation in the REC2Stim trial, these frequency bands have the priority in power band suppression. Also, spikes with a frequency rang of 10-80 Hz [38], that we could use as a surrogate marker for suppression of epileptic discharges, can be analysed with the chosen settings. Not being able to analyse the suppression in the lowest frequency bands is not problematic regarding the clinical application.

Whether the deviation from the baseline power was significant, was assessed with the bootstrap method (significance level 5%). The bootstrap method was useful to acquire a clear image, to simplify the identification of the suppression. However, using the bootstrap-method caused a loss of information. If a high amount of spontaneous activity is present before the stimulation, the average baseline has a high power. A post-stimulus suppression would therefore be a suppression relative to the high powered baseline. For the clinical application this limitation is not relevant, as the goal is to suppress the epileptiform activity (which means the baseline will probably have a high power in the epilepsy related frequency bands). However, it is relevant to understand why certain stimulations do not cause power suppression (e.g. when the signal during the one second prior to the stimulation was already suppressed compared to the overall ECoG signal. This could be an effect of IEDs [39].) Also, Figure 4.9 shows an image with and without bootstrapping. The lower image, without bootstrapping, shows high amounts of spontaneous activity before the stimulus (spikes and suppression in between). After stimulation a suppression in the frequency band < 50 Hz is visible. The suppression may or may not be a direct effect of the stimulation. This is not clear due to the spontaneous activity present before stimulation. In the upper image, with bootstrapping, this information is lost.

Functional area

For the clinical trial REC2Stim, a stimulation location outside functional area is desired. For the entire research population, a stimulation location was found outside functional area, for which suppression in the SOZ was observed. For five subjects, part of the grid was not stimulated during motor mapping. For two out of these five subjects the final optimal stimulation pair contained one electrode that was not stimulated during motor mapping. We do not expect this electrode to be part of functional area, but this cannot be ruled out.

3.4.3 Clinical implications

In the REC2Stim study, electrical pulses will be delivered to abort the build-up of a seizure and prevent the clinical seizure. The number of electrodes with suppression necessary to abort the seizure is yet unknown. The largest suppression we found, caused by one stimulus pair, was in 88% of the SOZ electrodes. The smallest suppression was only 9% of the SOZ electrodes, see Table 3.4. Besides the unknown necessary proportion of suppression in the SOZ, the total duration of suppression is also unidentified. As seen in both the time signal and TF images, the suppression does not last longer than 0.5-1 s (Figure 3.10). Regarding the frequency range which is suppressed: lower limit frequency median was 10 Hz, upper limit frequency median was 76 Hz, for all subjects combined (section 3.3.2). Therefore, the suppression covers (part of) the alpha rhythm, beta and gamma. As previously stated, this range is appropriate for the suppression of frequencies that increase during seizure onset.

The suppression observed in the time-frequency domain, can also be seen in the ECoG time signal. Figure 3.10 presents the time signal of the response in two different electrodes after SPES in the stimulation pair T30-T31. For this stimulation pair, ten consecutive stimulations were applied. The response to each of those individual stimulations is shown. Figure 3.10a shows a consistent response after each of the stimulations. A typical ER is described as a sharp N1 wave (10-50 ms), followed by a slow N2 wave (50-300 ms) [20, 40, 41],which is also what can be observed in this figure. It seems

as if the slow N2 wave, corresponds with the suppression observed in the TF domain. It is known that the ER has some variations. Some reports describe variety of polarities and latencies of the ER. E.g. N1 peak latency could exceed 50 ms and the N2 potential (peak latency of $>$ 100 ms) may occur alone [42, 43]. If an N2 wave occurs, without an N1 peak, it might seem as if a suppression is present without an ER. The electrode presented in Figure 3.10c (T40), does not show a similar response to the stimulation as in electrode T22. Ten inconsistent responses are observed. For some stimulations (3,4,8,10), a small slow N2 wave of an ER could be distinguished. In other stimulations (e.g. 2 and 6) there is no slow wave visible, but a flattening of the ECoG during the first half second. The peaks/sharp waves that were present before the stimulation are suppressed for a short period. The inconsistent responses in the same electrode after ten stimuli of the same stimulation pair, imply that the response is influenced by something else than location (e.g. the phase of the ECoG signal, see Chapter 4).

The association between ERs and SP has a clinical relevance as regards to decreasing the number of possible stimulation locations in the REC2Stim trial. ERs serve as a starting point for the stimulation location to abort seizures, but leaves us with many options as the SOZ is usually widely connected. Combining the electrodes in which both ER and SP were elicited decreases the potential locations. The electrodes containing an SP were not a perfect subset of the electrodes containing an ER. However, in 68% of the electrodes with an SP, an ER was found as well. The SP with an ER were found to be stronger. In 32% of the electrodes with an ER, an SP was found as well. Meaning, if only electrodes with an ER and SP would be considered, the total number of sites to analyse would be reduced with 68%.

3.4.4 Relation to other work

Other studies also describe suppressions after SPES [44, 39, 22]. In 2012, Alarcon et al analyzed activity of single neurons during IEDs and after SPES and identified four patterns: burst-only (lasting $<$ 100 ms), suppression-only (lasting 100-1300 ms), burst-suppression or no-change. These patterns were observed both during IEDs and after SPES. This suggests that IEDs and SPES trigger similar neurophysiological mechanisms probably initiated by brief synchronized burst firing in some cells followed by long inhibition. Interestingly, in the neurons showing suppression (burst-suppression or suppression-only) after stimulation, higher baseline firing rates were observed. We also saw that for stimuli after which a suppression was visible, the baseline signal sometimes contained more spikes/sharp waves than the other stimuli (e.g. Figure 3.10c). The median duration of suppression we observed was 200 ms (range 10-800 ms), which was slightly shorter than Alarcon et al. Alarcon states that the functional consequence of the long suppression periods remains uncertain. Whereas in some regions, such long periods of inhibition may protect from seizures, in others they may be the cause of rebound synchronization as a significant number of cells may start firing synchronously shortly after inhibition ceases. In particular, the existence of burst-suppression patterns imply that the same neuron can undergo suppression following burst firing, which might represent a protective mechanism against generalization.

Maliia et al. also described a burst-suppression pattern with early excitation (10-60 ms) of fast rhythms and a delayed inhibition (60-500 ms) induced by SPES. We did not find a delayed inhibition, but a median latency of the power suppression of 20 ms (range 10-160 ms). Maliia et al. found that in the delayed period, stimulation in the SOZ induced a higher inhibition in the epilepsy related higher frequencies (Ripples (100-250 Hz) and Fast-Ripples (250-100 Hz)) in all recorded brain areas, in all studied patients. In agreement with Maliia, Davis et al. also reports delayed high-frequency suppression (DHFS) elicited by SPES. DHFS was determined using the interval 0.4-1 s and 70-250 Hz post stimulation. DHFS was a significant feature of responses on electrodes inside the SOZ when stimulation was applied to adjacent or functionally connected electrodes. The response, when combined with objective analytic

techniques, provided a reliable marker of the SOZ in patients with refractory epilepsy. The estimated SOZ significantly identified the clinical SOZ in 6 out of 10 patients. We compared the number of suppressions in the SOZ electrodes with the non-SOZ electrodes in three subjects (B.2, B.8 and B.9), but we did not observe a significant difference of suppressions in the SOZ electrodes compared to the non-SOZ electrodes (chi-squared test $p>.05$). However, our purpose was not to use the suppressions for SOZ identification. We observed suppressions between 10-250 Hz, which also include the high frequencies Davis et al. observed. However, our median upper frequency limit was 76 Hz, which was in the high gamma band.

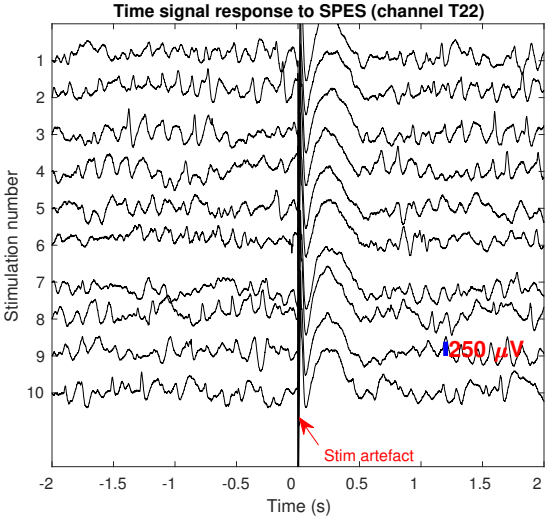
3.4.5 Future directions

In the time domain, a variable occurrence of suppressions in a response electrode after stimulation in the same stimulus pair was sometimes observed (Figure 3.10). The inconsistent response might be explained by a difference in phase at the moment of stimulation [23]. Further research is necessary to explore whether the phase of ECoG signals relate to the occurrence of suppression after stimulation.

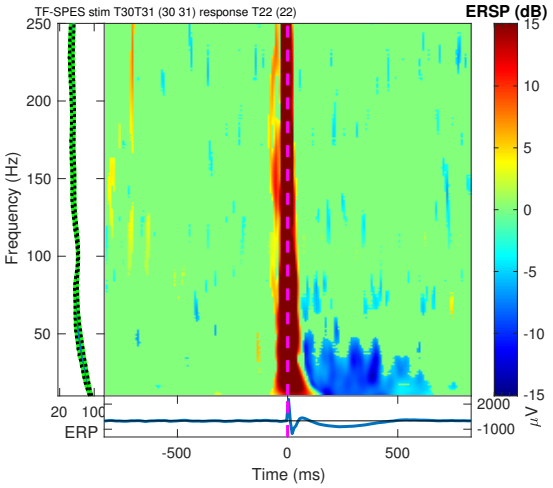
The nature of our research was to explore the occurrence of power suppressions and its use to diminish the number of potential stimulation pairs in the REC2Stim trial. The next step would be the understand the physiological meaning of the suppression. Mathematical models could be useful to simulate the neuronal behaviour after stimulation and the observed suppression. Hebbink et al. used a simple network model for simulations of the effect of epilepsy surgery on the seizure rate [45]. A similar network approach could be used to simulate the suppressions after stimulation and its effect on the seizure rate. More insight could be gained regarding to the connection between the stimulus pair and the response electrode showing the suppression. This might give us enough insight to determine its clinical use.

3.5 Conclusion

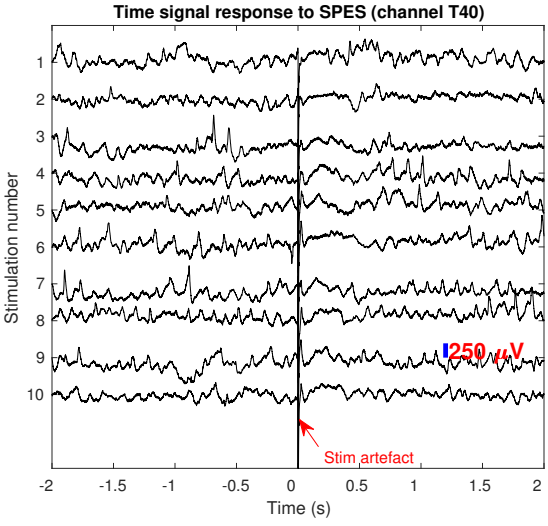
The occurrence of SP was strongly associated with the occurrence of ERs ($p<.001$), but the electrodes containing an SP were not a full subset of the electrodes in which an ER was elicited. A stimulus pair that causes suppression in (part of) the SOZ zone and is assumed to be connected to the SOZ (proven by an ER) was found in each subject. Further research is needed to investigate whether cortical stimulation, based on the stimulus pair suppressing power in the SOZ after SPES, is also effective in reducing epileptiform activity.



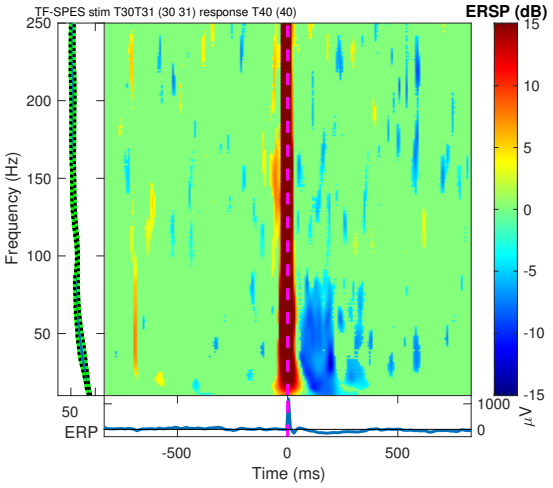
(a) The response to SPES in channel T22 is shown. The ECoG signal in time domain, shows a slow wave after each of the ten stimuli (an ER). Note that the spikes present in the pre-stimulus epoch, are absent during the first 500 ms post stimulus.



(b) The response to SPES in channel T22 in the TF decomposition is shown. The TF decomposition shows the suppression in the form of a blue spot during the same time window as the slow wave in the time domain.



(c) The response to SPES in channel T40 is shown. An inconsistent response after stimulation can be observed. Multiple spikes are visible before stimulation. In some electrodes, these spikes are shortly suppressed after stimulation



(d) The response to SPES in channel T40 in the time-frequency decomposition is shown. The suppression seen in some electrodes in the time domain, is seen as a blue spot in the TF domain during the first 250 ms.

Figure 3.10: Subject B.5. The figures present the response to SPES in the time domain and in the time frequency decomposition. The response in two different channels are shown after stimulation in the same stimulation pair (T30-T31). The response is measured in T22, which is located in the SOZ and functional area. The stimulation pair electrodes are located outside the SOZ and functional area.

Chapter 4

Power suppression and phase

Contents

4.1 Objectives

In the time domain, a variable occurrence of suppressions in a response electrode after stimulation in the same stimulus pair was sometimes observed (Figure 3.10). The inconsistent response might be explained by a difference in signal phase in the response electrode at the moment of stimulation [23]. Phase analysis can be performed based on different methods. Cheron et all. applied the inter trial coherence (ITC) in order to quantify the contribution of electroencephalographic oscillation in the generation of the frontal N30 component of the somatosensory evoked potentials (SSEP) triggered by median nerve electrical stimulation at the wrist [46]. We reproduced their method and compared the results to verify our ITC calculation method. Thereafter, we explored whether the phase of ECoG signals in the response electrodes relates to the occurrence of suppression after stimulation using the ITC. Usami et al. investigated modulation of cortical responses to input from distant areas by local spontaneous alpha/beta oscillations [47]. We explored whether this effect can be observed for SP, using the instantaneous phase in the response electrodes.

4.2 Methods

4.2.1 Subject characteristics

Two new subjects were added in this chapter, see Table 4.1. Subject C.1 underwent SSEP triggered by median nerve electrical stimulation at the wrist at the IEMU in the UMC Utrecht. Data of this patient was used for the ITC method verification in section 4.2.2. Subject C.2 was introduced for the phase analysis in section 4.2.3. This subject underwent SPES following the standard protocol in the UMC Utrecht. Another criteria was participation in the SPES science protocol, as this protocol executed 20 consecutive stimuli instead of 10 consecutive stimuli during the standard protocol. The increased number of stimuli was essential during phase analysis.

4.2.2 Phase method verification

Inter Trial Coherence (ITC)

The phase analysis in this section was performed using the inter trial coherence (ITC), also called the phase-locking value. The ITC was calculated using the MATLAB® function by EEGlab [28]. The ITC is

Table 4.1: Study population. SPES number refers to the number used in the UMC Utrecht. The abbreviations for the different grid locations are: C=central, sOc = sub occipital, T = temporal, sT = sub temporal.

Patient	Age/Sex	SPES code	Target	Grid Location	# Stimulus pairs/ electrodes
C.1	9/F	-	SSEP (method verification)	C	-/64
C.2	31/F	140	SPES phase analysis	T, sT, sOT, sOc	27/56

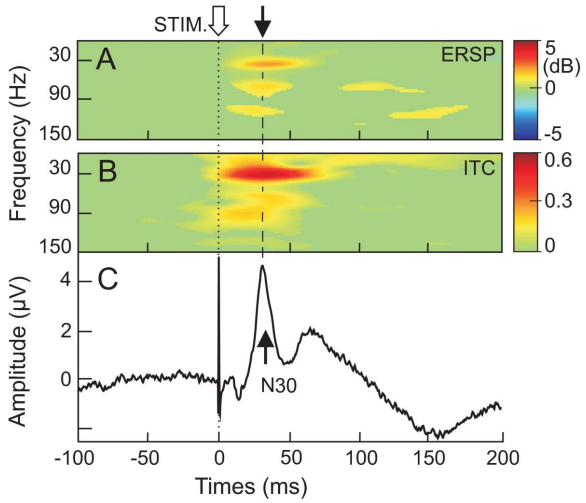
a frequency-domain measure of the synchronization of activity at a particular latency and frequency in different ECoG trials. Inter-trial phase coherence is defined by:

$$ITPC(f,t) = \frac{1}{n}\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|}, \tag{4.1}$$

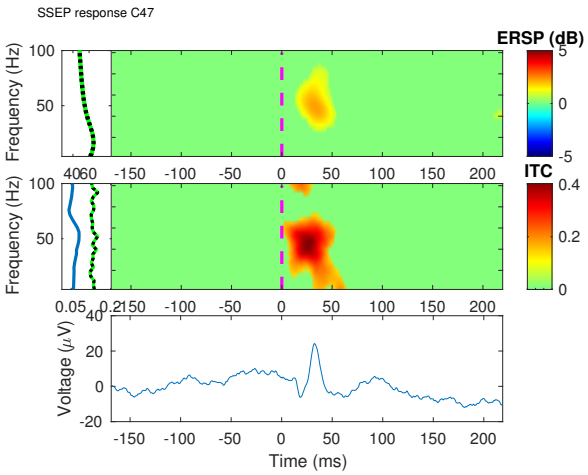
where $F_k(f,t)$ is the spectral estimate of trial k at frequency f and time t. To compute $F_k(f,t)$, the short-time Fourier transform was used. $|\ |$ represents the complex norm. The ITC has a range from 0 to 1, where 0 represents a lack of synchronisation between different trials and 1 represents perfect synchronization. As for the ERSP, significance of deviations from the baseline power was assessed using a bootstrap method (significance level 5%).

Findings

A total of 411 trials were obtained from subject C.1. Cheron et al. included 7 subjects, resulting in 3000 trials. The ERSP and ITC for one electrode are shown in Figure 4.1. The left image was computed by Cheron et al., and the right image was obtained by ourselves.



(a) The SSEP triggered by electrical stimulation of the median nerve recorded from F4. The peak of ERSP and ITC value is in the beta range (25-35 Hz) and coincides with the N30 latency peak. From: Cheron et al., BMC Neuroscience 2007 [46]



(b) The peak of ERSP and ITC value is in the gamma range (35-60 Hz). Also, the significant ERSP and ITC values coincide with the N30 latency peak in the time signal shown beneath the ITC.

Figure 4.1: ERSP and ITC of SSEP EEG **(a)** and ECoG **(b)** data. The same method performed by Cheron at al. **(a)** and ourselves **(b)**, in different patients.

In Figure 4.1a and b, a phase coherence is observed that coincides with the N30 latency peak in the time signal. Also a significant power increase in the ERSP image around the N30 peak is present. The frequency band in which this is the strongest differs in the two images We found a frequency range of 30-80 Hz, while Cheron et al. found a range of 30-100 Hz. As the findings are similar in both groups, we continued with the ITC for the phase analysis relevant for the power suppressions in the next section.

4.2.3 Phase analysis

Data processing

After network analysis of the clinical SPES, the stimulation pairs with the most outgoing connections (ERs), were stimulated a second time for a total of 20 stimuli (following the SPES science protocol in the UMC Utrecht, METC number: 15/342). These stimulation pairs with all recording electrodes were used for the phase analysis. The different steps of data processing are illustrated in Figure 4.2. Time frequency decompositions were computed as described in section 2.2.2, averaged for the 20 stimuli per stimulation pair and recording electrode combination (step 1). The SVM was used to detect SPs in all 1458 images, and visually checked afterwards (MvdS). The stimulation pair - recording electrode combinations in which no SP was detected, were removed from the analysis (step 2). For those in which an SP was detected, individual stimuli were used for TF image computation, meaning a total of 20 images for each stimulation pair - recording electrode combination. The individual images were computed using both bootstrapping and non bootstrapping settings (step 3). To determine the final analysis data set, these images were visually scored on the presence of an SP (MvdS/DvB). All images that the two observers disagreed upon were directly removed from the data set. First the images with bootstrapping were scored (step 4), see example in Figure 4.3. If an SP was present, the individual stimulus belonged to the *SP-present* group. If an SP was absent, the image without bootstrapping was assessed (step 5). If any suppression was present in that image, the response was considered ambiguous and the individual stimulus was removed to prevent the stimulus from littering the data set. If the image did not contain any suppression, the individual stimulus was addressed to the *SP-absent* group. The data processing resulted in two different groups for each stimulus pair - recording electrode combinations. E.g. stimulus pair A-B caused an SP in recording electrode C in four individual stimuli, which were placed in the *SP-present group*. The response in C after stimulation in stimulus pair A-B showed in five individual stimuli no suppression at all. These stimuli were placed in the *SP-absent group*. The remaining 11 stimuli were removed from the data set, either due to disagreement between the two observers, or diffuse suppression throughout the image, see example in Figure 4.2.

ITC calculation

For each stimulation pair - response electrode combination two groups originated during the data processing: the *SP-present* group and the *SP-absent* group. For both groups the ITC was computed. The baseline was set to [1 s - 400 ms] prior to the stimulus. Therefore, the baseline would not interfere with the period 400 ms - 10 ms prior to stimulation, as we are interested in the time period right before stimulation. It was decided not to use the post stimulus data as baseline, because the effect of the stimulus might effect the calculation of the phase before pre-stimulation. To analyse whether trials with a suppression have a phase coherence at the moment of stimulation, the ITC image right before stimulation in both groups was compared.

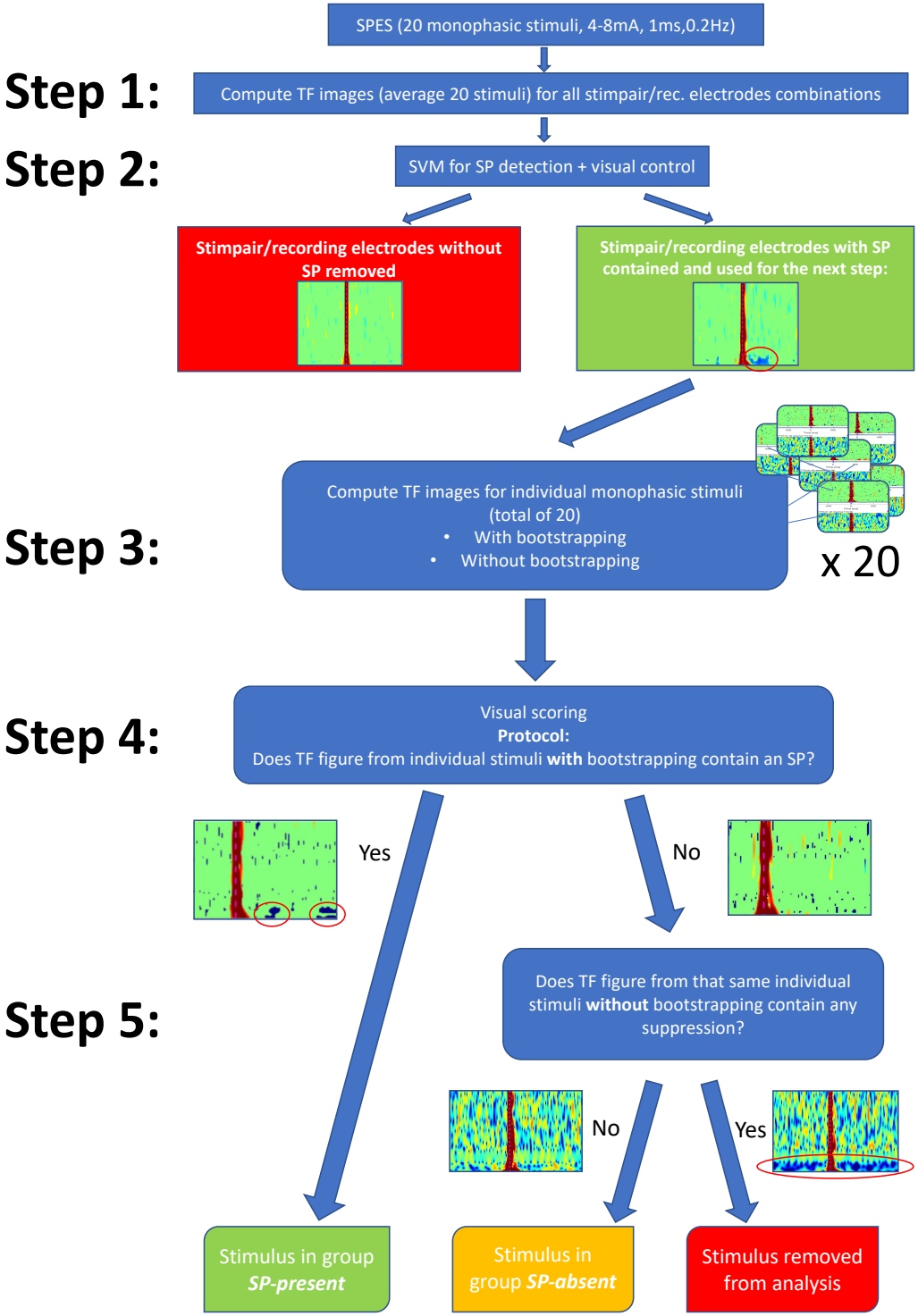
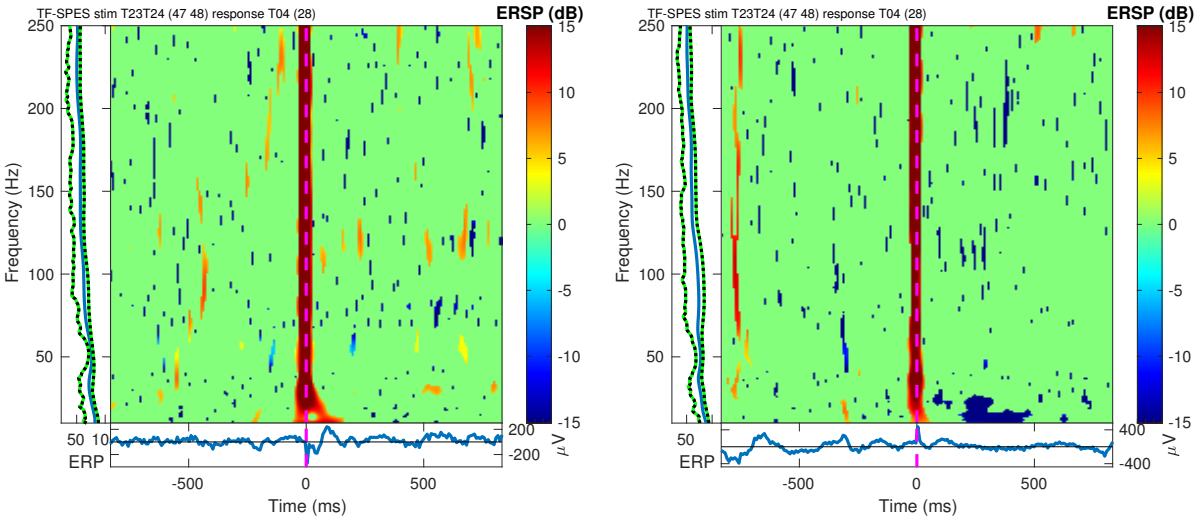


Figure 4.2: Flowchart representing the data processing steps



(a) TF image of an individual stimuli in which no SP can be observed.

(b) TF image of an individual stimuli in which a clear SP in the form of a blue spot is shown.

Figure 4.3: Example of individual stimuli (one out of twenty). Both images are a response in electrode T04 in the TF domain, after stimulation in the stimulus pair T23-T24.

Instantaneous phase

Another phase measure is the instantaneous phase determined by the Hilbert transform. For a signal s, the analytic signal ζ is a complex function of time defined as follows:

$$\zeta = s(t) + j\tilde{s}(t) = A(t)e^{j\phi(t)}, \tag{4.2}$$

where the function $\tilde{s}(t)$ is the Hilbert transform of $s(t)$. $A(t)$ and $\phi(t)$ are the instantaneous amplitude and instantaneous phase respectively of signal $s(t)$ [48]. The instantaneous phase was defined according to:

$$\phi(t) = arctan\left(\frac{\tilde{s}(t)}{s(t)}\right), \tag{4.3}$$

as described by [49]. The phase response is a constant $\frac{\pi}{2}$ lag at all frequencies. The instantaneous amplitude and phase have a clear physical meaning only if $s(t)$ is a narrow-band signal [48]. Therefore, a high- and low-pass [8 20] Hz FIR filter, order 60, was applied to the ECoG data. A FIR filter was preferable to an IIR filter due to modification of the stimulus artifact. The filter caused a phase delay of 30 samples, which was corrected in the filtered ECoG signal. The alpha-band (8-13 Hz) and low beta-band (13-20 Hz) were chosen, because alpha/beta oscillations have been hypothesized to gate local cortical processing. E.g. the phase of alpha and/or beta oscillations can modulate perceptual processing [50, 51, 52]. Dugué et al. observed that the phase of ongoing alpha (∼10 Hz) oscillations within 400 ms before a single TMS pulse significantly covaried with the perceptual outcome. This effect was observed in occipital regions around the site of TMS, as well as in a distant frontocentral region.

The instantaneous phase of the alpha/beta band was determined with the MATLAB® functions *hilbert* and *angle* every 5 ms, starting 60 ms up to 10 ms before stimulus. This includes the period right before stimulation, but excludes a possible stimulus artifact. *Hilbert* computed the hilbert transform defined in equation 4.2. *Angle* returned the phase angles in radians for each element in the hilbert transform as defined in equation 4.3. The phase lies between $-\pi$ and π. Consequently, the

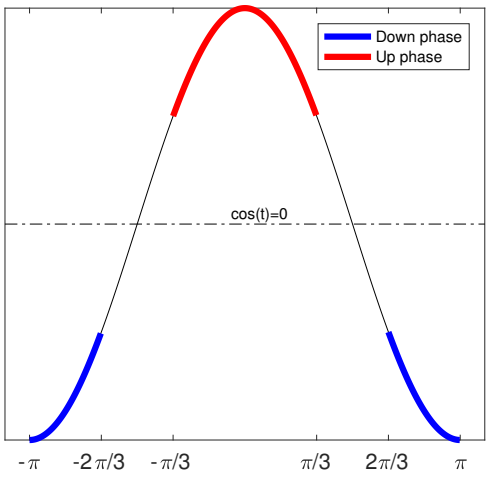


Figure 4.4: Division of trials in up or down phase presented by red or blue respectively.

phase was categorized as up phase ($-\frac{\pi}{3}$ till $\frac{\pi}{3}$), where $cos(t) > 0$ or down phase ($-\pi$ till $-\frac{\pi}{3}$ and $\frac{\pi}{3}$ till π), where $cos(t) < 0$ (see Figure 4.4). Trials that belonged to neither of the categories were discarded.

The trials were sorted in the same matter as the ITC calculation. However, the individual stimuli from all stimulus pairs were combined and divided according to presence of an SP, resulting in two groups. This is different from the ITC calculation, where the different stimulus pairs were analysed separately. This way, the pool of data was larger than during the ITC calculation.

In both groups the total number of stimuli which had an up or down phase for each time point [-60 to -10 ms] was determined. The ratio of the number of stimuli down/up phase was calculated and plotted. Furthermore, for each time instant, a chi-squared test was performed for statistical differences between both groups.

At last, the continuous instantaneous phase ($-\pi$ to π) was assessed for both groups. A Mann-Whitney U test was performed to determine statistical significance.

4.3 Results

4.3.1 Phase analysis

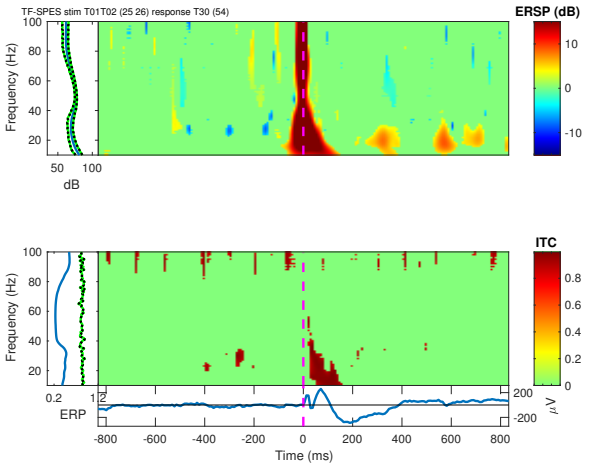
Data processing

In total 674 individual stimuli (responses) were included after data processing. 376 stimuli in the *SP-present group* and 298 stimuli in the *SP-absent group*. The number of stimulus pairs was 21. A stimulus pair elicited an SP in on average four response electrodes (range 1-9). The median number of stimuli within each stimulus-recording electrode combination group was five (range 2-10).

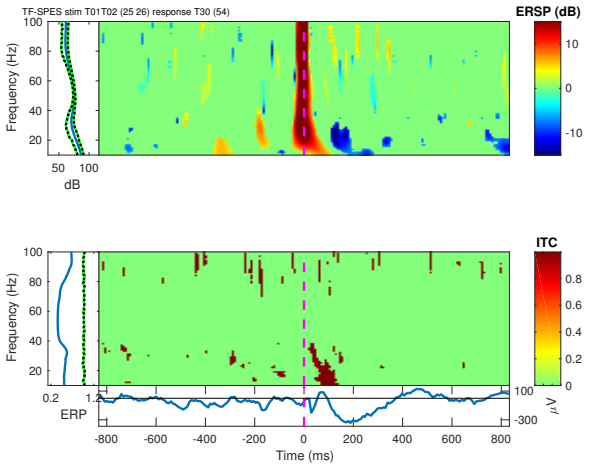
ITC

Figure 4.5 shows the ERSP and ITC for the response in T30 after stimulating T01-T02. Figure 4.5b was computed based on trials with an SP, which can be seen in the ERSP image, showing the SP. The

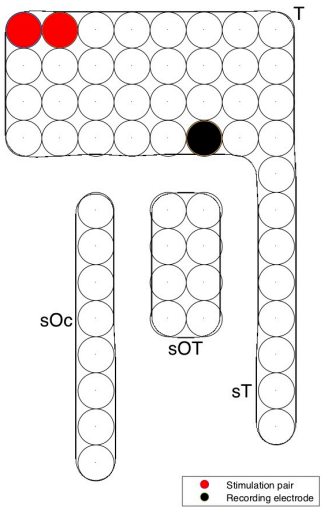
SP is absent in Figure 4.5a. Both images show a significant coherence right after stimulation. However, neither of the images shows a coherence right before stimulation.



(a) Response for the combined stimuli in which an SP was not present. In the ERSP image, no sign of suppression is seen. The ITC shows a significant coherence between the trials after stimulation. Right before stimulation, no significant coherence is observed.



(b) Response for the combined stimuli in which an SP was present. The ERSP shows a blue spot after stimulation, indicating a suppression in these trials. A coherence is shown in the ITC image, after stimulation. Right before applying the stimulus, no coherence can be observed.



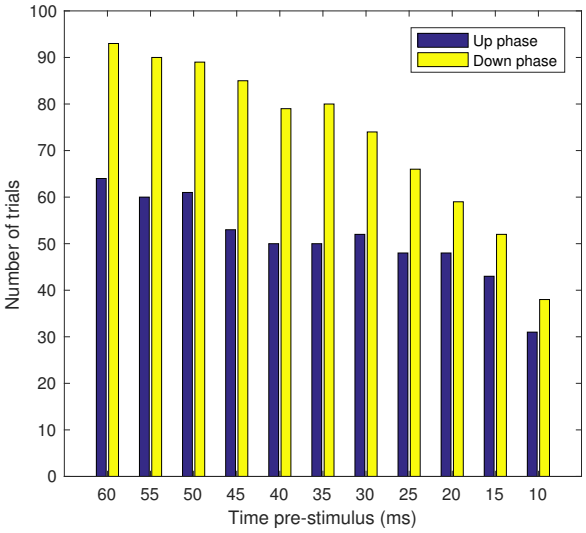
(c) Schematic grid of subject C.2. The red electrodes are used as stimulus pair in the ITC images in (a) and (b). The black electrode is the corresponding response electrode.

Figure 4.5: The images represent the response in T30 after stimulation in stimulus pair T01T02, shown in (a) and (b). The schematic representation of the grid is shown in figure (c).

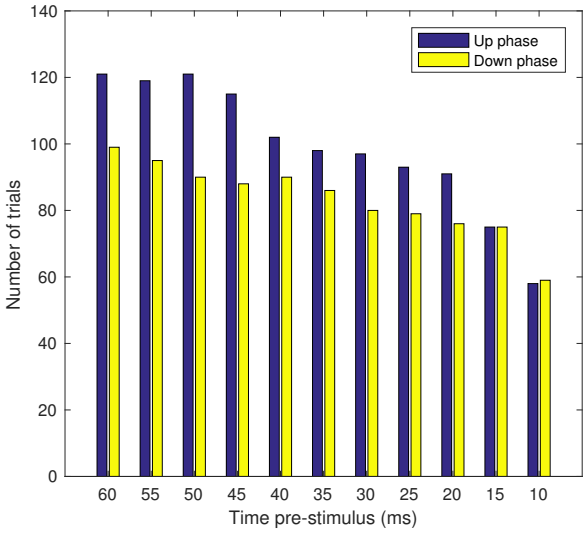
Instantaneous phase

The distribution of the instantaneous phase for the trials with an SP and the trials without an SP is displayed in Figure 4.6. If an SP was not present, the phase was more often categorized as down phase for all time points. If an SP was present, the category with the most trials fluctuated through time. During 60-20 ms pre stimulus, the majority of the trials were found with an up phase. This changed at 15 ms pre stimulus, where both categories had equal trials. Figure 4.7 shows the ratio between the number of trials in both categories (down phase / up phase) for each time point. The ratio is higher when an SP is not present for each time point and although decreasing when approaching the stimulation time, remains larger than 1. This compared to the trials in which an SP was present, where the ratio is below 1 from 60 ms pre-stimulus until 20 ms pre-stimulus. A chi-squared test showed a statistical difference in distribution for 60 up until 25 ms pre-stimulus ($p<.05$).

Besides a distribution between up and down phase, the continuous instantaneous phase ($-\pi$ to π) was assessed in both groups. Figure 4.8 presents the difference in median and interquartile ranges. A larger phase was found for time instances 50-35 pre-stimulus if an SP was not present ($p<.05$). This did not hold statistically for the other pre-stimulus moments.



(a) All individual trials without an SP. For each time instant, the majority belongs to the down phase group. The difference decreases as the stimulus approaches.



(b) All individual trials with an SP. For 60-20 ms pre stimulus, the majority belongs to the up phase group. At 15 ms pre stimulus, both groups are equal.

Figure 4.6: From 60 ms to 10 ms pre-stimulus with an interval of 5 ms, the instantaneous phase was computed. The phase was categorized as up phase ($-\frac{\pi}{3}$ till $\frac{\pi}{3}$) or down phase ($-\pi$ till $-\frac{\pi}{3}$ and $\frac{\pi}{3}$ till π).

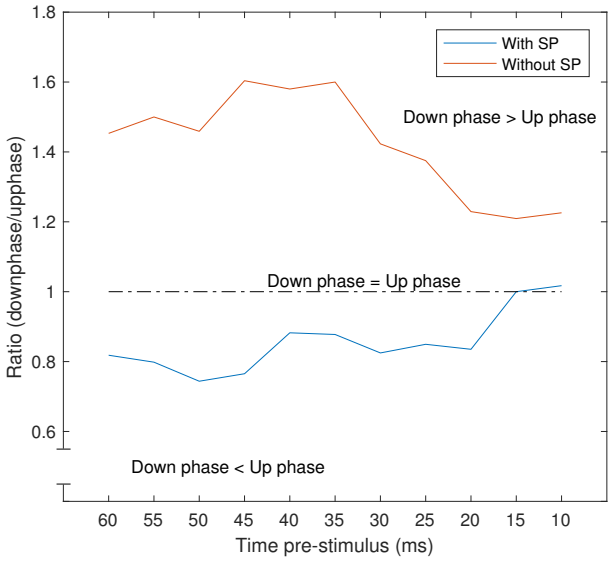


Figure 4.7: Ratio between the number of trials in the down phase versus the up phase during 50ms pre-stimulus. The ratio in both groups grows nearer as the stimulus approaches.

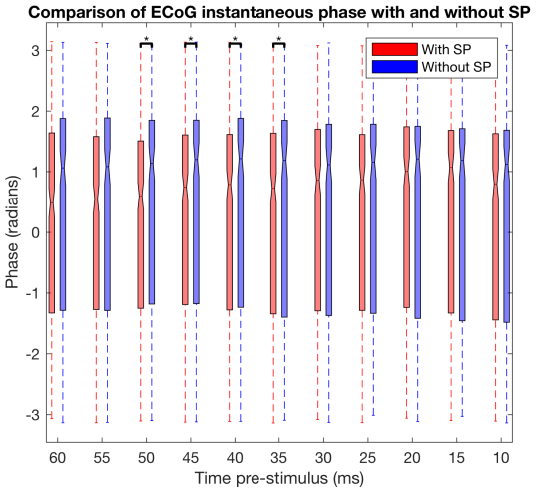


Figure 4.8: Boxplots showing difference in the instantaneous phase between trials with and without an SP for different time instants pre-stimulus. $*$:p$<$.05, tested with the Mann-Whitney U test.

4.4 Discussion

We explored whether the phase of ECoG signals relates to the occurrence of suppression after stimulation. To gain more insight, we compared the responses of individual stimulations with and without an SP.

4.4.1 Interpretation results

ITC

We expected that the individual trials in which a suppression was observed might have a similar phase at the moment of stimulation. Therefore, the ITC right before stimulation is expected to be higher in

the trials with a suppression compared to the trials without suppression. However, in Figure 4.5 this difference was not observed. Both images show a phase coherence after stimulation, but not before stimulation. Small amount of available data per stimulus electrode could explain a lack of significant coherence; this is further addressed in section 4.4.2. Furthermore, it could be possible that not one specific phase is necessary for power suppression, but a range of phases could cause the response. The coherence after stimulation seems to be related to the ER that is visible in both groups. The ER is more prominent in the stimuli without suppression, and therefore shows a higher coherence. The post-stimulus SP does not seem to cause an increased ITC.

Instantaneous phase

For the calculation of the instantaneous phase using the Hilbert transform, all stimulation pairs were combined. Therefore, a larger pool of data could be analysed. In general, a difference in distribution of the up and down phase seems to be present when comparing the trials with and without an SP. When an SP was present, more trials had an up phase from 60 up until 20 ms pre-stimulus in the ECoG signal containing frequency components between 8-20 Hz. For the trials without an SP, the opposite was found (60-10 ms). For both groups, the number of trials satisfying the conditions of either of the groups diminished when approaching the stimulus. A FIR filter was chosen to minimize interference of the stimulation artifact after filtering. However, the last 15 ms before the stimulation were still slightly affected by the stimulus artifact. Therefore, the phase at 15 and 10 ms pre-stimulus are unreliable. It might explain why the proportion of up and down phase in both groups approach each other near the end and a $p > .05$ was achieved for these time instants. Also the diminished number of trials belonging to the up or down phase could be explained by this.

4.4.2 Methodological aspects

For each subject 20 consecutive stimuli were given per stimulation pair. In none of the subjects all 20 stimuli were included in the data set, due to disagreement between the observers and littered stimuli with diffuse suppression (see lower image in Figure 4.9). For some subjects only two stimuli remained in one of the two groups. These small number hamper a proper evaluation. Computation of ITC typically required a large amount of trials (e.g. [46] for EEG data). As none of the subjects who underwent the SPES science protocol at the UMC Utrecht had more than 20 stimuli, we thought it was not useful to include any more subjects.

Furthermore, both Cheron et al. and Usami et al. isolated modulation by power and phase. To establish an independent effect either by power or by phase, trials were sorted by the average of alpha/beta power or by phase (Usami). Cheron combined trials for which the EEG amplitude of the filtered signal measured around the N30 latency remained similar compared to the pre-stimulus amplitude for analysis of the phase effect. We did not incorporate such criterion as the amount of trials was too small. Also the trials with a post-stimulus suppression, will by definition not have the same power as pre-stimulus.

4.4.3 Relation to other work

Usami et al. investigated cortical responses to input from distant areas modulated by local spontaneous alpha/beta oscillations. They also included medically refractory epilepsy patients with grid and depth electrodes implanted. They used SPES (biphasic wave pulse: 0.3ms duration, interval 3-3.6 s, intensity 0.5-1 mA) to elicit CCEPs. The effect of local oscillatory power and phase on CCEPs was measured. They found a modulation by the power but did not observe reproducible phase effects on CCEPs. However, they state it is difficult to definitively rule out the effects, because lack of significant phase effects can arise from inadequate temporal precision when estimating the phase at which stimuli were delivered. They sampled the data at 1 kHz in three patients and at 2 kHz in two patients, which is similar to

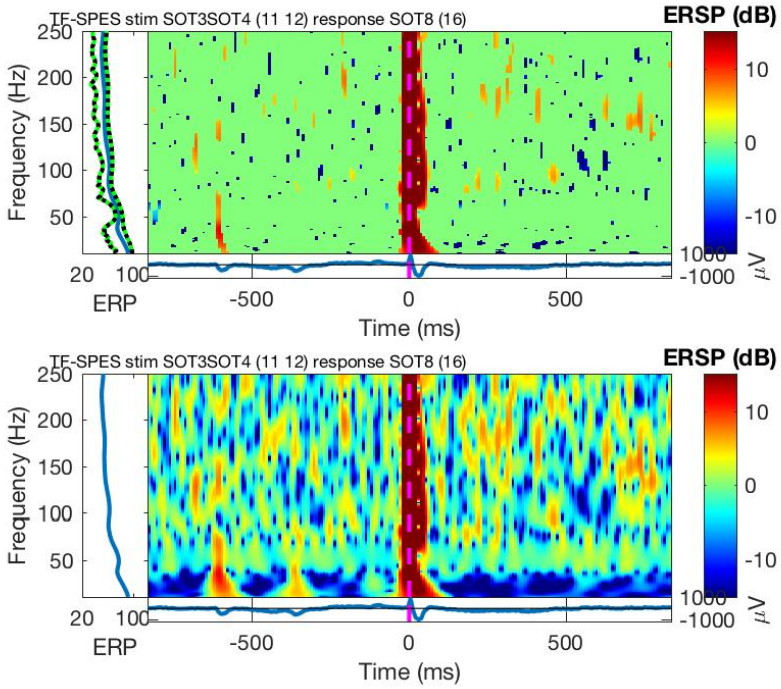


Figure 4.9: Both TF images are computed for response electrode sOT8 after stimulation in stimulus pair sOT3-sOT4. The upper image was constructed using the bootstrap method with a significance level of 5%. The lower image was constructed without the bootstrap method. Therefore, more variability is seen in the image.

our sampling frequency of 2048 Hz. Also, temporal jitter in the effect of stimulation on local neuronal activity could apply [47]. We did find a phase effect for the occurrence of an SP using a similar method in one subject.

4.4.4 Future directions

To gain more insight in the phase influence on suppression as a response after SPES, more stimuli per stimulus pair are necessary. During the science SPES protocol, 20 stimuli were executed. For the phase analysis, more stimuli should be included.

As the instantaneous phase showed a difference in distribution between the up and down phase, it could be useful to investigate this effect in more subjects.

To investigate the ITC right before stimulation, the baseline was set to [1 s - 400 ms] pre-stimulus. A longer baseline interval could be chosen if it involves a period around three seconds after stimulation, as the inter-stimulus interval is five seconds.

4.5 Conclusion

The sample size (n=1) was too small to identify significance in phase coherence right before stimulation. Nevertheless, we observed a different distribution of trials in the up or down phase for responses with and without an SP. This was significant at 60-25 ms pre-stimulus ($p<.05$). Also, a difference was observed

for the continuous phase at 50-35 ms pre-stimulus ($p<.05$). Further research is necessary to be decisive about the influence of the phase on the occurrence of power suppression after SPES.

Chapter 5

General Discussion

5.1 Interpretation results

We observed an SP in the TF decomposition images after applying SPES in medically refractory epilepsy patients. The SP was associated with the underlying ER effective network ($p < .001$). In one subject, the majority of the trials were found in the down phase when an SP was absent, compared to the up phase when an SP was present. Whether the occurrence of SP is dependent on the pre-stimulus phase has not yet been established due to lack of data.

5.2 Relation to other work

Chapter 3 shows that the SP does not always consistently appear in a response electrode after stimulation in the same stimulus pair. Therefore, the occurrence of the suppression is not only determined by the location of the stimulus pair and response electrode. The stochastic nature of SP resembles that of DRs, that are not always seen in an electrode after each stimulus applied in the same stimulus pair [15, 20]. Valentin et al. hypothesized that DRs could be explained by the presence of a cortical loop in the epileptogenic cortex as they are evoked with a latency between 100 ms and 1 s. This loop would be activated by afferents from the stimulated cortex, allowing for a build-up of activity or recruitment of neurons until an epileptiform discharge is triggered. An abnormal control of cortical activity, probably due to an altered balance between excitation and inhibition could explain the existence of a DR. When the stimulus intensity was increased, the morphology of DRs was not clearly modified, but a higher probability of occurrence was observed [15, 27]. Similar mechanisms can play a role in the existence of SP. They do not speculate on a possible explanation why this loop sometimes is and sometimes is not activated by stimulation of the same stimulus pair.

5.3 Methodological aspects

Using the SVM for automatic detection of an SP, still requires visual inspection to ensure that only true suppressed power responses are used for further analysis. This is time consuming. Still, an average of 677 images (SD 548) per subject were visually checked, instead of 3409 images (SD 1475) per subject, a reduction of 80%.

Suppression of power was observed in both time domain and time-frequency decomposition (Figure 3.10). Therefore, it is unlikely that the SP is an artifact of our time-frequency decomposition method. However, we need to be careful with the interpretation of the TF decomposition images. The images are computed using the average of the baseline. A time-frequency pixel is either suppressed, elevated or equal to the average value of the baseline. Therefore, the ERSP TF images are all relative numbers and no absolute values. This makes the time domain less susceptible to methodological influences than the TF images. As (automated) detection of the SP in the time domain will be difficult, an alternative method could be to include absolute TF images besides the ERSP images.

When using the bootstrap method, each pixel value is being assessed and compared to the significance threshold. The significance threshold is established per frequency sample. An example is shown in Figure 4.9. The upper image was computed using the bootstrap method, with a significance level of 5%. Most of the image is green, as only little of the pixels crossed the threshold. The lower image was computed without using the bootstrap method. In the frequencies below 50 Hz, there are some spikes (10-80) Hz followed by periods of suppression. Also the post stimulus period is suppressed. This pattern resembles the spontaneous interictal epileptiform discharges and the suppression in firing observed by Alarcon et al. [39]. However, this information is lost after bootstrapping.

A concrete definition for an SP has not yet been established. They were observed in different shapes and sizes. Stating which responses contained an SP was therefore subjective in some cases.

5.4 Clinical implications

In one subject the majority of the trials were found in the up phase if an SP was present. For the clinical implication this means that phase controlled stimulation could enlarge the chance of seizure abortion, if SP is a marker for suppression of epileptiform activity.

5.5 Future directions

A definite method to find the optimal stimulation pair in the REC2Stim study remains unestablished. However, we have established a potential stimulation pair per subject, taking into account both ERs and SP as criterion. Thereby diminishing the number of potential stimulation locations. Nevertheless, the implication of the power suppressions observed after SPES regarding the abortion of seizures remains speculation.

Chapter 6

General Conclusion

We explored the suppression phenomenon observed in TF images after applying SPES in a phenomenological manner. In all ten subjects SP was detected. As there was no proven method for detection of SP, we developed with SVM a detection algorithm with a sensitivity of 0.82 and specificity of 0.86, using its area and duration as features. An association between the occurrence of an SP in a response electrode and the underlying connection to the stimulus pair was established. For all ten subjects we could identify a stimulus pair that caused an SP and had a functional connection with part of the SOZ. We hypothesized that SP might serve as a surrogate marker for suppression of epileptiform activity and could therefore indicate the preferred site of cortical network stimulation. The REC2Stim trial will provide the necessary proof to determine if the hypothesize is justified. In one subject we where not able to identify a significant inter trial coherence right before stimulation in stimuli with an SP. Nevertheless, we observed a different distribution of trials in the up or down phase for responses with and without an SP.

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