Cortical electrical stimulation in epilepsy patients

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Cortical electrical stimulation in epilepsy patients

Corticale elektrische stimulatie bij patiënten met epilepsie

(met een samenvatting in het Nederlands)

Proefschrift

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Dorien van Blooijs

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Promotor:
Prof. dr. N.F. Ramsey

Copromotoren:
Dr. F.S.S. Leijten
Dr. D. Hermes

Beoordelingscommissie:
Prof. dr. K.P.J. Braun
Prof. dr. C. Kemner (voorzitter)
Prof. dr. P.R. Schuurman
Dr. E.C.W. van Straaten
Prof. dr. G.J.M. Zijlmans

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GENERAL INTRODUCTION

General introduction

The incentive for this thesis was the clinical dilemma of a specific set of patients with difficult-to-treat epilepsy who presented themselves to the outpatient clinic of the UMC Utrecht. These patients had epilepsy confined to the eloquent pericentral primary sensorimotor cortex. The primary sensory motor cortex (Brodmann areas 1-4) shares a unique anatomical and physiological structure and is a predilection site for specific epileptogenic pathologies e.g. focal cortical dysplasia. These lesions are strongly associated with drug-resistant epilepsy. Symptomatic seizures in the primary sensorimotor cortex are convulsive and are known for their long duration, sometimes resulting in epilepsia partialis continua (EPC) with uninterrupted twitches in a limb for days to years. Seizure frequency is typically high, often with multiple daily seizures showing visible contractions and jerking which has a large impact on quality of life [1].

What are the current treatment options for epilepsy patients?

The ultimate treatment goal for epilepsy patients is cessation of all seizures. The first treatment option is prescription of anti-seizure medication. When two or more anti-seizure medications have been appropriately administered and fail to achieve seizure freedom, the patient is considered to have drug-resistant epilepsy [2]. Around 30% of people with epilepsy remain drug-resistant [3]. When the patient has epilepsy arising from a focal region, the patient may benefit from surgical resection of the region responsible for these epileptic seizures, defined as the epileptogenic region [4]. Pre-surgical evaluation to localize the epileptogenic region consists of non-invasive methods, such as electro-encephalography (EEG), magnetic resonance imaging (MRI), positron-emission-tomography (PET) and magneto-encephalography (MEG). When the epileptogenic region is near eloquent cortex or non-invasive methods have not been able to sufficiently localize the epileptogenic region, intracranial recordings with electrocorticography (ECoG) or stereo-EEG (sEEG) are used to delineate the epileptogenic region in more detail. After implantation of these intracranial electrodes, a patient is monitored for a variable period of three days to three weeks. During this monitoring period, clinicians await spontaneous seizures to localize the seizure onset zone (SOZ), which is the brain tissue showing the first changes in electrical activity at the start of a seizure. Additionally, electrical stimulation mapping can be applied to delineate eloquent cortex involved in speech, vision, sensory or motor function, which cannot be resected without the risk of neurological deficits after surgery.

In patients with epilepsy arising from the primary sensorimotor cortex, epilepsy surgery is rarely an attractive option. In a study of 52 patients who underwent surgical resection in

the primary sensorimotor cortex, neurological deficits were induced in 50% and only 31% became seizure-free after surgery [5]. Since expected function loss due to resection often outweighs potential benefits, surgical resection is often avoided or constrained to spare function [6,7]. Multiple subpial transections as a surgical, function-sparing alternative rarely renders patients seizure free (16% according to [8]). This means that seizure freedom is hard to achieve in this specific group of patients. It is therefore important to find an alternative therapy which reduces seizure frequency without inducing neurological deficits.

Electrical stimulation as treatment for epilepsy patients

Over the last decade, neuromodulatory therapy of epileptic seizures has become available as a treatment option when anti-seizure medication turns out ineffective and epilepsy surgery is not feasible or does not lead to seizure freedom. The goal of electrical stimulation as therapy is twofold: to abort seizures and to modify the mechanisms leading to seizures [9]. A variety of working mechanisms have been suggested: a stabilizing reduction of local excitability [10], induction of plasticity by short-term or long-term depression of synaptic responses [11], stimulus-dependent changes in ion channel molecules, regulating the balance of excitation and inhibition [12], raising the seizure threshold [13], modification of synaptic effectiveness by long-term potentiation [14], reduction of network excitability by an adenosine mediated process [15] and extracellular potassium transients which affect a range of cellular processes involved in seizures [9]. The specific effects of electrical stimulation at the single-cell, synapse, and network level will vary depending on the stimulation site and stimulation parameters.

Neurostimulation can be applied in a non-invasive and invasive manner. Examples of non-invasive neurostimulation are transcranial magnetic stimulation (TMS) and transcranial direct current electrical stimulation (tDCS). TMS is often used in research to induce inhibitory effects, and is sometimes used to treat epilepsy, requiring frequent hospital visits. Effects seem to be transient [16]. Epilepsy treatment with tDCS also varies in efficacy (44-89%), while reported follow-up duration is short (1-3 months) [16].

A better approach to treat epilepsy might be to apply neurostimulation in the long-term, which means that an implantable device is needed. Examples of invasive neuromodulation with an implantable device are deep brain stimulation (DBS), vagal nerve stimulation (VNS), and cortical stimulation (CS). Chronic electrical stimulation therapies in epilepsy have traditionally targeted the whole brain through sites connected to widespread cortical regions, such as the vagal nerve (in VNS) and the anterior nucleus of the thalamus (in DBS) [17–19]. With these global stimulation therapies, there is no need to localize a cortical seizure focus, since stimulation is applied in a larger network, and, like anti-seizure medication, reaches the whole brain. Seizure freedom is rarely achieved and

therefore, the aim is seizure frequency reduction with more than 50%, which is achieved in 40-55% of the patients [11,18,20]. Adverse effects with VNS include hoarseness (up to 62% of patients), cough and local paresthesia or pain (5-25% of patients), and aggravation of sleep breathing disorders (in 28-57% of the patients) [20]. Adverse effects with DBS include depression (15% of the patients in the SANTE trial [21]) and memory impairment (in 13% of the patients). These adverse effects often decrease with reduced stimulation intensity, but might even persist after interruption of therapy [20].

With cortical stimulation, seizure focus localization is key, since this is usually the site where stimulation is applied (local stimulation). Targeting only the specific brain region involved in seizure generation may avoid any unwanted systemic side effects of global stimulation. Adverse effects with local stimulation depend on the site where this local stimulation is applied; e.g. motor performance might be affected when applying local stimulation in the primary motor cortex. Seizure frequency reduction generally turns out higher in local stimulation (86%) than in global stimulation (40%) [11]. Efficacy and the number of responders increase over time with both stimulation techniques [22].

Open-loop and closed-loop stimulation

Stimulation can be applied in two modalities: open-loop and closed-loop (see Figure 1). With open-loop stimulation, electrical pulses are administered at pre-programmed time points, either continuously or intermittently, and independent of ongoing neuronal activity [23,24]. The idea of cyclic open-loop stimulation is to interfere with any ongoing epileptiform activity in order to prevent the development of a seizure [22]. Another hypothesis is that open-loop stimulation would lead to alterations in network characteristics that reduce the capability of the brain to evoke epileptic seizures [25]. Yet, others, more critical of open-loop stimulation, argue that open-loop stimulation would lead to an alteration in synaptic efficacy in the affected region, changing network characteristics in a potentially deleterious way, e.g. kindling new seizure activity. This could also result in alteration of normal brain function [26]. A few case studies with in total 21 patients have shown efficacy using open-loop cortical stimulation in the primary sensorimotor cortex [1,6,7,27–30]. These patients were successfully treated with seizure frequency reductions ranging from 75-90% without any reported side-effects.

With closed-loop stimulation, electrical pulses are only applied in response to detection of a certain event, like a seizure or interictal epileptic activity. The largest clinical trial investigating closed-loop stimulation was conducted by Neuropace [22,31]. 191 patients were included with various seizure onset locations of whom 59% achieved a more than 50% seizure reduction. Although open-loop stimulation comes out favorably in a few case studies, there may be a substantial publication bias, with

only twenty-one cases reported, compared to hundreds who underwent closed-loop stimulation [31]. One of the advantages of closed-loop stimulation is the minimization of side effects related to stimulation when there are no seizures [9]. Furthermore, closed-loop stimulation minimizes power consumption and delivers a lower total daily dose of current, which both benefits battery life of the neurostimulator [9].

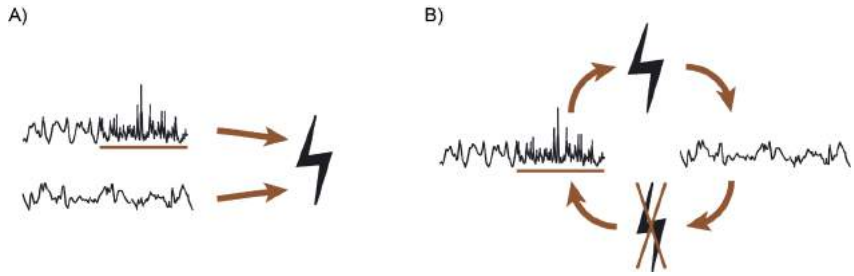

Figure 1: Two modalities of electrical stimulation. A) Open-loop stimulation: electrical pulses are administered at pre-programmed time points, either continuously or intermittently, and independent of ongoing neuronal activity. B) Closed-loop stimulation: electrical pulses are only applied in response to detection of a certain event, like a seizure (underlined signal) or interictal epileptic activity.

In both the case studies and the Neuropace trial, stimulation was applied in the seizure onset region. However, when onset is located in the primary sensorimotor cortex, the problem is that electrical stimulation in this eloquent area might cause adverse side effects. No stimulation-related adverse effects, such as involuntary motor activity or decreased motor performance were reported when stimulation involved the primary motor cortex [32]. This was not supported by observations during stimulation itself or by functional assessments, but by the fact that no adverse effects were reported. Patients with motor seizures may not notice the stimulation effect on performance, because they usually already experience decreased performance due to the seizures themselves. This may explain why no adverse events were reported, while stimulation may still have affected motor function. It has been shown that therapeutic studies often underestimate side-effects when seizure outcome is the main focus and that judging adverse events requires detailed interrogation [33]. Moreover, a small (0.1 mA) increase in current intensity may induce visible contractions and seizures, especially in the limb representation part of the sensorimotor cortex [34,35]. Furthermore, the current intensity threshold of electrical stimulation, that induces after-discharges leading to seizures, is much lower in the primary motor cortex (0.5-4 mA) compared to other cortical areas, e.g. Broca's area (7-15 mA), limiting the range of effective current intensities to choose from. Stimulation at the seizure onset region may seem most straightforward, but clinicians,

performing electrical stimulation mapping to delineate eloquent cortex, recognize the difficulty of stimulating the motor cortex without inducing adverse effects. This leaves us with the question where electrical stimulation could be applied in the specific set of patients with epilepsy arising from the primary sensorimotor cortex.

Brain networks

In the last decades, the idea of a single epileptogenic region generating epileptic seizures has evolved into the concept of epilepsy as a network disease, as specific changes in network topology have been revealed in epilepsy patients [36,37]. Epileptogenesis refers to the development from a normal neuronal network into a hyperexcitable network that is capable of evoking spontaneous, recurrent seizures [38,39]. Neuronal loss, neurogenesis, glial loss, gliogenesis, axonal and dendritic plasticity and intracellular channelopathies or receptor dysfunction are some of the underlying mechanisms. Investigating brain networks is important to gain insight in epileptogenesis and how seizures evolve.

Brain networks can be studied with three types of analyses: structural, functional and effective connectivity analyses [40]. Structural connectivity analyses are based on white matter tracts analyzed with e.g. Diffusion Tensor Imaging (DTI) [41] or with histology in post-mortem studies [42]. Functional connectivity analyses focus on statistical dependencies, and can be measured by the level of coherence between brain areas. These are often analyzed with (intracranial) EEG, MEG or functional MRI [36]. Effective connectivity analysis refers to causal interactions and this can be measured by applying a (electric) perturbation to one brain area and tracking the evoked responses in other brain areas.

Single Pulse Electrical Stimulation (SPES, see Figure 2A) is such an electrical stimulation protocol that can be executed to investigate effective connectivity of brain networks. The SPES protocol consists of electrical pulses (repetition rate 0.1 – 1 Hz) of short lasting current stimuli (2-8 mA, pulse width <=1 ms) delivered to adjacent electrodes that are either part of intracranial grids (ECoG) or depth electrodes (sEEG) implanted in epilepsy patients for presurgical evaluation. Early studies using such a protocol aimed at confirming specific functional cortical connections in networks of the language and motor systems [43,44], or the fronto-temporal network [45], by means of the cortico-cortical evoked potential (CCEP) [46]. This CCEP consists of an early negative deflection within 100 ms after stimulation (N1, see Figure 2B) [47], followed by a slow wave (N2). The N1 peak likely represents the summation of direct cortico-cortical impulses conveyed both by small fibers with slower conduction velocities and by large, myelinated fibers activated through indirect oligo-synaptic cortico-cortical projections [48]. SPES seems to generate both direct and indirect orthodromic discharges at the site of stimulation [44,49] via a direct corticocortical pathway and an indirect cortico-subcortico-cortical pathway.

In a study by Enatsu et al., properties of the CCEP were proposed that relate to epilepsy itself [50,51]. They found that N1 amplitudes were significantly larger in the area of ictal propagation than outside this area. Others found accentuated N1 amplitudes in the SOZ [52,53] or that when stimulating the SOZ, CCEPs occurred more often in areas of seizure propagation [54]. The latter approach has widened to analysis of CCEPs in order to define effective networks, with properties that are common in functional network analysis.

In network analysis, complex brain networks are represented by nodes which represent brain regions, and edges which represent connections between two nodes [36]. Network measures are used to characterize how complex brain networks are organized [55] and how these networks are affected in patients with epilepsy. The two most straightforward measures are the indegree, and the outdegree [56]. The indegree is the number of edges towards a node, and the outdegree is the number of edges going from a node. In patients who became seizure-free after surgery, the electrode with the highest outdegree was reported to be indicative of localizing the epileptogenic region [57]. Other network measures that estimate the importance of a node in a network are the betweenness centrality, and the clustering coefficient. These measures identify nodes that play an important role in integrating network modules [56]. Compared to healthy controls, patients with epilepsy have an increased clustering coefficient [58] and a decreased betweenness centrality [59]. This is taken to indicate a more segregated network, in which fast exchange of information throughout the brain is compromised [58]. Perhaps, this explains some of the cognitive deficits that accompany chronic epilepsy. The changes in brain networks in patients with epilepsy might give some starting points to investigate cortical network stimulation as a long-term neurostimulation therapy.

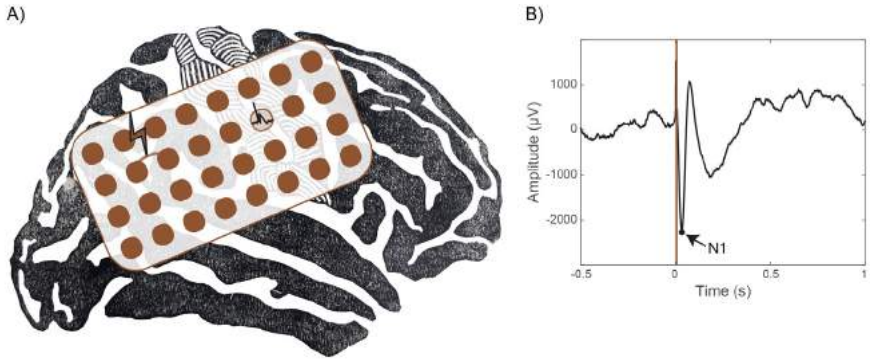

Figure 2: Single Pulse Electrical Stimulation. *A) The brain is covered with a subdural electrode grid (ECoG). Single Pulse Electrical Stimuli are applied to each electrode pair. Ten responses to stimulation are averaged to increase the signal-to-noise-ratio. Responses in those averaged epochs of other electrodes are detected. B) An example of a cortico-cortical evoked potential (CCEP). The vertical brown bar at t = 0 s indicates the stimulus artefact. The first negative deflection after the stimulus artefact is called the N1-peak.*

Aim and outline of this thesis

We aim to provide a new therapy for patients with epilepsy arising from the primary sensorimotor cortex. Seizures arising in the primary sensorimotor cortex present a high clinical burden, due to the disabling motor seizures, high frequency of these seizures and lack of surgical treatment options. Due to the localization of the SOZ, resection is not possible without inducing motor impairment. Invasive electrical stimulation is a promising technique that has evolved rapidly in the past decade. Local electrical stimulation, like cortical stimulation, is more effective in seizure frequency reduction than global electrical stimulation, such as DBS or VNS. Since the epileptogenic region can be well delineated in patients with epilepsy located in the primary sensorimotor cortex, local electrical stimulation might be preferred. However, stimulation in the primary sensorimotor cortex cannot be applied without inducing side effects affecting motor function. This raises the question whether we could apply electrical stimulation in a site connected with the epileptogenic region affecting ictal activity: cortical network stimulation. We hypothesized that stimulation in an area with a proven connection with the (primary sensorimotor) epileptogenic focus will reduce seizure frequency and severity without negative effects on sensorimotor functions. When a neuronal network may develop into a hyperexcitable network liable to evoke seizures, we envision that we might revert this epileptogenic process, e.g. with long-term neurostimulation. This thesis is subdivided into three parts.

Part 1: characteristics of effective connectivity in brain networks

The first part of this thesis focuses on the characteristics of effective connectivity in brain networks derived from SPES. Before cortical network stimulation can be applied as a therapy for epilepsy patients, it is important to further investigate the characteristics of an effective connectivity derived from SPES with a focus on the potential application of selecting the site of electrical stimulation therapy. Little is known about the differences between connections in and outside the epileptogenic region, and whether we could expect many connections towards the epileptogenic region. With many connections, other criteria might become relevant to determine a stimulation site connected with the epileptogenic focus. With only a few connections, SPES might not be the best tool to determine a stimulation site for cortical network stimulation therapy. In **Chapter 2**, we compared effective connectivity within and outside epileptogenic areas.

We could envision that a stimulation site for electrical stimulation therapy would be determined during the surgery when the neurostimulator is implanted. Most

research investigating effective connectivity is executed in the awake patient. We need to understand how these networks are affected by anesthesia and whether we could expect a similar effective network as in the awake patient when determining a stimulation site under anesthesia. In Chapter 3, we performed SPES in the operating room and investigated the effect of anesthetics on effective connectivity.

When electrical stimulation therapy is effective in the individual patient, this therapy can be applied for a long period of time and should remain as effective after many years. Furthermore, determination of the stimulation site with a connection towards the epileptogenic zone should not be affected by patient characteristics like age. It is therefore important to understand how brain networks change with age. In Chapter 4, we studied these networks in a population 4-51 years of age and investigated how the transmission speed in white matter tracts changes with age.

Part 2: neurostimulation as treatment for epilepsy patients

The second part of this thesis addresses treatment of epilepsy patients with neurostimulation. Electrical stimulation therapy can be applied with two modalities: closed-loop and open-loop stimulation. Since both modalities are used in the epilepsy patient population, we need to compare both modalities and determine the preferred modality for cortical network stimulation. In Chapter 5, we review several studies using open-loop or closed-loop stimulation to treat epilepsy patients and describe the success rates and side effects.

With SPES, electrical stimulation with short pulses is applied and these single pulses might lead to transient effects on interictal activity. This might provide us with a surrogate marker which could help us determine the optimal stimulation site for neurostimulation treatment. In Chapter 6, we analyzed the transient changes in interictal activity while applying SPES.

The aforementioned studies led to the conception and execution of a clinical trial on closed-loop cortical network stimulation: the "Rational Extra-eloquent Closed-loop Cortical Stimulation"-study (REC2Stim). In Chapter 7, we describe this early feasibility study in which we implanted five patients with a neurostimulator and applied closed-loop cortical network stimulation to reduce seizure frequency.

Part 3: transition towards open science

These studies laid the foundation for closed-loop cortical network stimulation as a clinical treatment option. However, we need more research to improve this neurostimulation therapy and make it available for a larger patient population. This progression might be enhanced by combining data from several studies and applying

artificial intelligence to predict what kind of therapy works for which individual patient. To further enhance the scientific developments towards optimized therapies for epilepsy patients, we prioritized organizing our unique intracranial EEG data. In the third part, we describe a practical workflow for organizing clinical intracranial EEG epilepsy data into the Brain Imaging Data Structure (BIDS) in Chapter 8.

In Chapter 9 and 10, I summarize and discuss the findings reported in this thesis and give recommendations for future research.

PART 1: CHARACTERISTICS OF EFFECTIVE CONNECTIVITY IN BRAIN NETWORKS

EVOKED DIRECTIONAL NETWORK CHARACTERISTICS OF EPILEPTOGENIC TISSUE DERIVED FROM SINGLE PULSE ELECTRICAL STIMULATION

Evoked directional network characteristics of epileptogenic tissue derived from Single Pulse Electrical Stimulation

D. van Blooijs, F.S.S. Leijten, P.C. van Rijen, H.G.E. Meijer, G.J.M. Huiskamp

Hum Brain Mapp. 2018; 39: 4611–4622.

Abstract

Objective: We investigated effective networks constructed from Single Pulse Electrical Stimulation (SPES) in epilepsy patients who underwent intracranial electrocorticography (ECoG). Using graph analysis, we compared network characteristics of tissue within and outside the epileptogenic area.

Methods: In 21 patients with subdural electrode grids (1 cm interelectrode distance), we constructed a binary, directional network derived from SPES early responses (<100 ms). We calculated indegree, outdegree, betweenness centrality, the percentage of bidirectional, receiving and activating connections, and the percentage of connections towards the (non-) epileptogenic tissue for each node in the network. We analyzed whether these network measures were significantly different in seizure onset zone (SOZ)-electrodes compared to non-SOZ electrodes, in resected area (RA)-electrodes compared to non-RA electrodes, and in seizure free compared to not-seizure free patients.

Results: Electrodes in the SOZ/RA showed significantly higher values for indegree and outdegree, both at group level, and at patient level, and more so in seizure free patients. These differences were not observed for betweenness centrality. There were also more bidirectional and fewer receiving connections in the SOZ/RA in seizure free patients. It appears that the SOZ/RA is densely connected with itself, with only little input arriving from non-SOZ/non-RA electrodes.

Conclusion: These results suggest that meso-scale effective network measures are different in epileptogenic compared to normal brain tissue. Local connections within the SOZ/RA are increased and the SOZ/RA is relatively isolated from the surrounding cortex.

Significance: This offers the prospect of enhanced prediction of epilepsy-prone brain areas using SPES.

Introduction

Epilepsy surgery is a highly effective therapy in selected people with focal epilepsy. In patients without a clear lesion on MRI, or with a lesion potentially overlapping with eloquent cortex, chronic intracranial electrocorticography (ECoG) monitoring may be necessary to delineate the seizure onset zone (SOZ). The SOZ is defined as the region from which epileptic seizures arise, and is assumed to be an important part of the epileptogenic zone, removal of which should stop seizures [4]. Ictal ECoG provides the gold standard for localizing this SOZ which is characterized by a recruiting seizure rhythm preceding or coinciding with the first clinical signs of a seizure. Waiting for spontaneous seizures usually determines the length of the monitoring period, and may require days to weeks, with stress for the patient and risks of complications like intracranial infections or hemorrhage.

Single Pulse Electrical Stimulation (SPES) is a clinical method for identifying the epileptogenic zone independent of spontaneous seizures, mainly because of the ability to provoke delayed responses (DRs) [47,60]. During the SPES protocol, electrocortical stimuli are systematically applied to pairs of adjacent electrodes on the subdural electrode grid and correlated responses in all other electrodes are analyzed. SPES can thus be used to reveal the physiological connections of cortical patches underlying the grid-electrodes and has the potential to contribute to our understanding of the network basis of epilepsy on a mesoscale [61]. Within 100 ms after the stimulus, early responses (ERs) may be observed after SPES, suggesting physiological connections from cortex under the stimulated electrode pair to cortex under the electrodes in which ERs are observed [61]. ERs occur each time a pulse is applied to the same electrode pair, and are thus deterministic. In cortico-cortical evoked potential (CCEP) studies, this ER is known as the N1-response [43,44,51,62] and the physiological networks derived from these N1-responses have been investigated in, for example, the language and motor system [43,44].

Physiological networks may be altered in brain diseases like epilepsy. Over the last decade, the concept of focal epilepsy as a localized region of abnormality has evolved into a concept of diseased cortical networks with nodes and connections also affected in regions away from the SOZ [36,58,63–66]. In the context of epilepsy surgery, the focus on defining only a local SOZ is disputed, since the whole brain network operates together, as is clear from the expression of seizures [64]. It has been suggested that seizure freedom may be best achieved by removing a critical part of tissue that interrupts the epileptic network [67].

In epilepsy research, networks have been reconstructed with data from fMRI, DTI, MEG, EEG, or intracranial EEG, from ictal, pre-ictal or interictal periods, at different

scales and with different methodological approaches. A network consists of nodes and edges. Nodes represent functional or structural elements of the network [68], or in case of SPES, a cortical patch underneath an ECoG electrode. Edges represent a connection between two areas.

Networks can be categorized as anatomical, functional, or effective networks. Anatomical networks are derived from structural axonal bundles between different brain regions [40]. Functional networks assess connectivity based on statistical dependencies between neuronal activity at different locations. Effective networks describe the causal interactions between neural elements caused by perturbation experiments like stimulation or SPES.

With graph analysis, the overall network characteristics can be quantified. Examples of commonly used graph measures are degree and betweenness centrality. The degree of a node is equal to the number of edges connected to that node. This value reflects the importance of an individual node in the network. The degree has a straightforward neurobiological interpretation: nodes with a high degree interact with many other nodes in the network. The degree can be directional and characterized as in- and outdegree; i.e. the number of incoming connections, or outgoing connections, respectively [69].

The betweenness centrality is defined as the fraction of all shortest paths between nodes in the network that pass through a given node [36,55]. Nodes connecting different parts of the network often have a high betweenness centrality [55]. In other words, betweenness centrality is a measure of the "importance" of a node to transfer information across the network. Unlike other measures that quantify network properties for a node, the betweenness centrality depends not only on the primary efferent and afferent connections to a node, but also on the secondary and tertiary connections [70].

Both for functional and anatomical networks, graph analysis has been applied extensively in epilepsy research. For instance, Van Mierlo et al. [57] constructed a directed functional connectivity graph during seizure onset in intracerebral EEG using the adaptive directed transfer function, from which they concluded that the electrode with the highest outdegree coincided best with the SOZ. Van Diessen et al. 2016 [59] demonstrated in scalp EEG-data that interictal network alterations are present in epilepsy patients. They showed that the betweenness centrality was overall significantly lower in networks of children with focal epilepsies compared to healthy children.

Analysis of SPES networks has revealed information by location and amplitude of evoked ERs. Mouthaan et al. [54] found high counts of ERs in the SOZ. Enatsu et al. [50] showed that the amplitude of ERs in and outside the SOZ was higher when a stimulus was applied within the SOZ. Boido et al. [71] categorized electrodes as "activator", "receiver" or "bidirectional contact" based on the number of evoked

ERs in and by each electrode. Activators were electrodes with many outgoing connections, receivers were electrodes with many ingoing connections, and a bidirectional contact had many in- and outgoing connections. They found a significant association between bidirectional electrodes and the SOZ.

So far, SPES networks have shown that location and amplitude are important measures for distinguishing the epileptogenic tissue, but this has not been analyzed in terms of network measures. In the present study, we combine analysis of the SPES network and the common network measures indegree, outdegree, and betweenness centrality to investigate the properties of epileptogenic tissue using the SPES network. Furthermore, we analyze the directionality of connections [71], and the destination of connections. Specifically, we investigate whether network characteristics are different in presumed epileptogenic tissue. We therefore constructed effective networks based on SPES ERs recorded during interictal periods collected in patients with focal epilepsy undergoing pre-surgical evaluation.

Materials and methods

Patients

We included patients who underwent long-term clinical ECoG monitoring preceding epilepsy surgery between 2014-2016 in whom Single Pulse Electrical Stimulation (SPES) was routinely performed for clinical decision making with stimuli applied in at least 90% of the electrodes. Patients who did not undergo resection were excluded. There was no overlap with patients included in previous studies by our group [54,60]. Patients had been admitted to the Intensive Epilepsy Monitoring Unit of the University Medical Centre of Utrecht, the Netherlands. All patients gave their informed consent and the entire investigation was performed under the ethical committee's approval under Dutch law.

Electrocorticography

Chronic ECoG was performed with subdural electrode grids (2-8 x 8) and strips (1x8 electrodes) placed directly on the cortex. They consisted of platinum circular electrodes embedded in silicone that had a 4.2 mm^2 contact surface and an inter-electrode distance of 1 cm. In four patients, also depth electrodes were implanted consisting of six cylindrical contacts with 7.9 mm^2 contact surface at a 5 mm inter-electrode distance (Ad-Tech, Racine, WI, USA).

Seizure onset zone and resected area

Two neurologists (CF, FL) localized the seizure onset zone (SOZ) and projected

the resected area (RA) on the grids in each patient. The SOZ was considered as the site with the earliest ictal activity, defined as patterns consisting of rhythmic spikes, sharp waves, spike and slow wave complexes, or recruiting gamma or beta activity. The RA usually contained the SOZ, but was sometimes larger because it included a lesion. Therefore, we used both areas as gold standards. We realize that we mentioned in the Introduction that the concept of epilepsy as a network disease has evolved, and still define a particular epileptogenic area.

Single pulse data acquisition

SPES was performed during ECoG monitoring with ECoG data sampled at 2048 Hz to enable visualization of evoked activity up to 500 Hz [60] using a MicroMed LTM64/128 express EEG headbox with integrated programmable stimulator (MicroMed, Mogliano - Veneto, Italy). Ten monophasic stimuli of 1 ms pulse width were applied at a frequency of 0.2 Hz to two adjacent electrodes. A current intensity of 8 mA was used, but in case of twitches or pain, the intensity was lowered to 4 mA. SPES results were taken from the total number of electrode pairs (#trials) to which ten pulses were applied. Results from clinical SPES and evoked delayed responses were used for the final clinical decision making in individual patients [60].

Analysis of early responses (ERs)

For each electrode, ten epochs with a time window of 2 s pre-stimulus to 3 s post-stimulus, time-locked to the stimulus, were averaged for each trial. Each epoch was corrected for baseline (a time window of 2 s prior to stimulation). ERs were determined with an automatic detector in each averaged epoch. ERs were detected within 9-100 ms, when a peak exceeded the threshold of 2.5 times the standard deviation measured during baseline (Figure 1). The detected ERs were visually checked (DvB). Electrodes which overlapped with another grid, or were noisy, were not stimulated and therefore excluded from analysis.

Constructing a nodal network

In traditional functional networks, each electrode is represented by one node of the network [72]. Since stimuli in SPES are applied to stimulus pairs, such nodes had to be defined differently. ERs originate from stimulus pairs (two electrodes), and are observed in single electrodes. We adapted the SPES-network to define a nodal network. When a stimulus pair evoked an ER in another electrode, both electrodes in the stimulus pair were assumed to project onto the electrode in which an ER was observed.

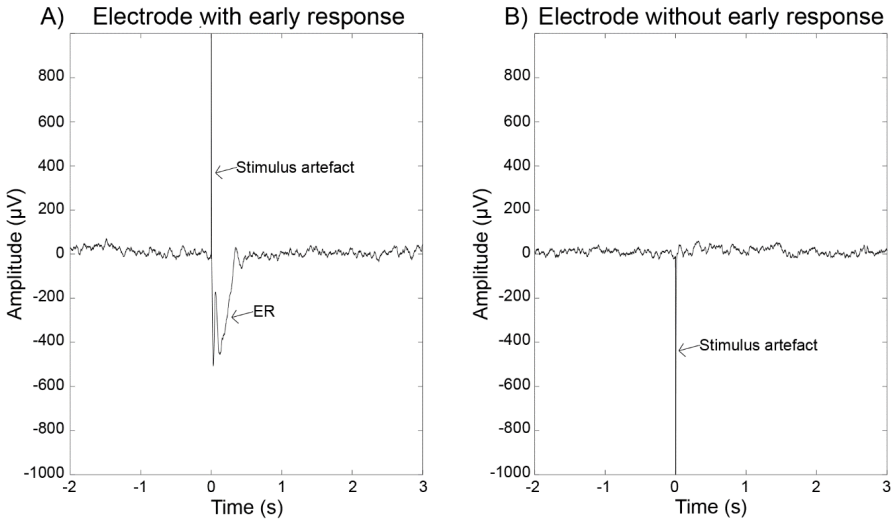

Figure 1: Visual check of epochs in which an ER was detected. *Ten epochs were averaged, resulting in one signal for each stimulus pair-response electrode combination. The left figure shows an averaged response in electrode 9 to stimulation of electrode pair 1-2. The straight line is the stimulus artefact, the ensuing negative wave the early response. The right figure shows an averaged response in electrode 5 to stimulating the same electrode pair. No ER is observed.*

Outdegree

Some electrodes were part of one stimulus pair, while others were part of two pairs. For example: electrode 1 was involved only in stimulus pair 1-2, whereas electrode 2 was involved in both 1-2 and 2-3. In electrode 1, the odds of detecting connections to other electrodes is half the chance of detecting connections to other electrodes in electrode 2 (Figure 2). Therefore, we normalized the number of ERs evoked by stimulating a specific electrode (outdegree: $e_{ER\rightarrow}$) by dividing it by the maximal possible outgoing connections (n_{out_total}) , defined as: the number of trials in which the specific electrode is stimulated (t_e) multiplied by the total number of potential response electrodes (e_{tot}) minus 2 (the number of electrodes in a stimulus pair) (Equation 1).

Indegree

When a stimulus is applied to an electrode, no ER can be detected in this electrode. Therefore, in an electrode stimulated once, an ER can be observed in one more trial, compared to electrodes stimulated twice. For example: an ER cannot be observed in electrode 1 only when stimulating 1-2, whereas an ER cannot be observed in electrode 2 when stimulating 1-2 and 2-3 (Figure 2). We normalized the number of ERs evoked in a specific electrode (indegree: $e_{ER\rightarrow}$) by dividing it by the maximum

possible incoming connections (n_{in_total}), defined as: 2 (the number of electrodes in a stimulus pair), multiplied by the total number of trials (t_{tot}) minus the number of trials in which the specific electrode was stimulated (t_e) (Equation 2).

Betweenness centrality

We normalized the betweenness centrality in each electrode (BC_e) (Equation 3) by dividing it by the maximum number of incoming connections (n_{in_total}) and the maximum number of outgoing connections (n_{out_total}) as defined previously.

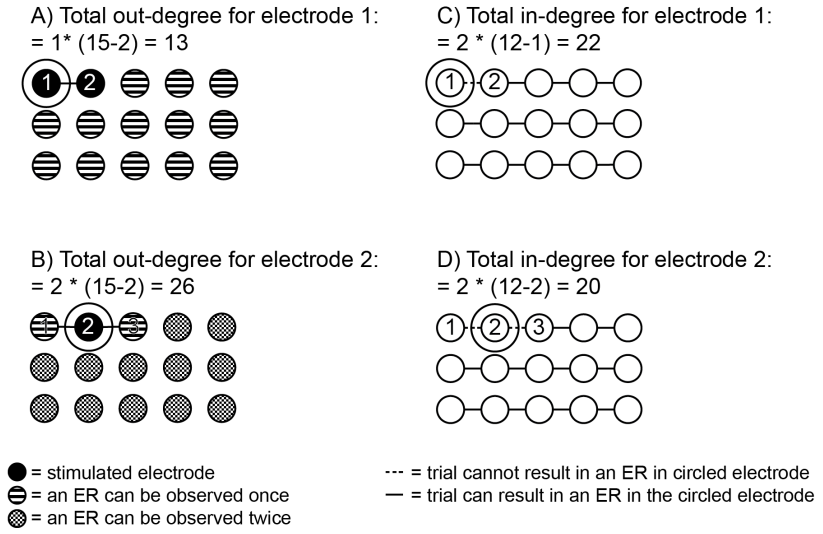

Figure 2: The difference in total out- and indegree for electrodes stimulated once or twice. Outdegree: *A) a stimulus is applied only once to electrode 1 (electrode-pair 1-2). In all other electrodes, an ER can be evoked only once. The maximal outdegree is the total number of electrodes minus the 2 electrodes in the stimulus pair, resulting in a maximal outdegree of 13. B) Electrode 2 is stimulated twice (as part of electrode-pairs 1-2 and 2-3). Therefore, the maximal outdegree is two times the total number of electrodes minus the two electrodes in the stimulus pair, resulting in a maximal outdegree of 26.* ***Indegree:*** *C) a total number of 12 trials with different stimulation pairs are applied in this example. Each trial can evoke an ER in a response electrode. In electrode 1, only 1 trial is applied. This results in a maximal indegree of two times the total number of trials minus the trials evolving the response electrode, resulting in a maximal indegree of 22. D) In electrode 2, two trials are applied, resulting in a maximal indegree of 20.*

The modified measures are given by the following equations. They range between 0-1, where 0 meant that no connections were observed, and 1 meant that all possible connections were observed.

Equation 1: outdegree of node

$$n_{outdegree} = \frac{e_{ER\rightarrow}}{t_e\ (e_{tot}\ -\ 2)}$$

Equation 2: indegree of node

$$n_{indegree} = \frac{e_{\rightarrow ER}}{2(t_{tot} - t_e)}$$

Equation 3: betweenness centrality in node

$$n_{BC} = \frac{BC_e}{n_{in\_total} n_{out\_total}} = \frac{BC_e}{\big(2(t_{tot} - t_e)\big)\big(\ t_e(e_{tot}\ -\ 2)\big)}$$

Network measures in (non-)SOZ and (non-)RA

Per patient, we divided the electrodes into two groups: SOZ and non-SOZ electrodes, RA and non-RA electrodes. We determined whether differences in network measures between those regions were statistically significant ($p<0.05$) using a Mann-Whitney U test.

We repeated the Mann-Whitney U test to determine statistical differences between the same groups ($p<0.05$) over all patients, and also for patients with Engel I and patients who were not-seizure free after surgery.

Directionality of connections in each node

After interpretation of the results from the first analysis, we proceeded in studying the directionality of connections.

We classified these connections into bidirectional, activating (connections towards other nodes), and receiving (connections from other nodes) (Boido et al., 2014). Per patient, over all patients, and in seizure free or not-seizure free patients, we determined whether there was a difference in directionality in SOZ -and non-SOZ nodes, and in RA- and non-RA nodes using a Mann-Whitney U test.

Then we looked at *the destination of connections from in and outside RA/SOZ*. We calculated the ratio of connections from a specific node to the (non-)RA from the total number of outgoing connections involving each specific node. We compared the ratio of connections from the (non-) RA to both the RA nodes and non-RA nodes using a Mann-Whitney U test. We repeated this test for the SOZ nodes and in patients with Engel I and patients who were not-seizure free after surgery.

Results

Patient characteristics

In total, 26 patients underwent grid monitoring between January 2014 and March 2016 (Table 1). Three patients did not undergo epilepsy surgery, because the SOZ

could not be determined. Two patients were excluded because less than 90% of the electrodes were stimulated with SPES. Thus, 21 patients (11 females, 10 males), with a median age of 15 years (range: 4-49 years) were included. Six patients were not-seizure free; 15 patients were seizure free after 1 year (Engel class Ia or Ib). ECoG involved a median number of 64 stimulated electrodes per patient (range: 48-86). The SOZ and RA were covered by a median number of 4.5 electrodes (range: 1-16) and 12 electrodes (range: 3-28) respectively. In each patient, a median number of 55 trials (range: 44-73) was applied.

Analysis – network measures in SOZ and RA

Table 1: Patient characteristics. In the number of electrodes, electrodes SOZ/RA, only stimulated electrodes are included, * indicates the patients where SOZ was not completely resected. ND= not determined. In 5 patients, the SOZ could not be delineated due to diffuse seizure onset (patient 2, 8, 16, 21) or status epilepticus during monitoring period (patient 17). Resection was then based on the location of a lesion on MRI. M=male, Fe=female, F=frontal, C=central, T=temporal, P=parietal, Oc= Occipital, IH=interhemispherical, D = depth electrode, Y=yes, N=no

Patient #	Age	Sex	Grid location	#Electrodes	#Trials	#Electrodes SOZ	#Electrodes RA	Seizure free?
1	6	Fe	T, Oc	54	46	1	13	Y
2	10	Fe	F, C, D	66	55	ND	13	Y
3	15	M	T, P, Oc	54	45	8 *	13	Y
4	42	Fe	T, P, Oc	75	64	4	22	Y
5	4	M	P, IH	55	47	3	9	Y
6	15	Fe	F, C	63	55	12 *	6	Y
7	19	M	T, Oc	77	64	10 *	13	N
8	25	Fe	T, P	70	60	ND	3	N
9	12	Fe	C, IH, D	48	40	10	12	Y
10	9	Fe	F, T, IH, C	80	70	16	19	Y
11	16	M	F, T, Oc, D	64	54	0	1	Y
12	49	M	C, T, P, Oc	67	62	7	9	Y
13	11	M	C	62	54	5 *	9	N
14	13	M	P, C, IH, D	61	53	4 *	16	Y
15	41	Fe	T	51	44	3	11	Y
16	14	Fe	F, C, T, IH	86	73	ND	15	Y
17	8	Fe	T, P, Oc	79	66	ND	28	N
18	18	M	C, IH	64	56	3	9	Y
19	15	Fe	C	60	51	2	10	Y
20	10	M	F, T, P	77	65	7 *	10	N
21	19	M	T, F	62	51	ND	16	N

Indegree (Figure 3 A)

In four patients (6, 9, 12, 18), the indegree was higher in the SOZ compared to nodes in non-SOZ. These patients all became seizure free. In nine patients (1, 2, 4, 5, 6, 9, 13, 15, 16), the indegree was higher in the RA, compared to non-RA nodes. Eight of these patients (all except 13) were seizure free after surgery. In patient 7, the indegree was lower in the RA and SOZ, compared to non-RA and non-SOZ nodes. This patient was not-seizure free after surgery.

When nodes of all patients were combined, the indegree was higher in both the SOZ ($p=0.01$, data not shown) and RA ($p<0.001$).

When we compared the group of patients with a good seizure outcome with the patients who were not-seizure free (Figure 5 A), the indegree was higher in the RA and SOZ compared with non-epileptogenic tissue in the seizure free group (respectively, $p<0.001$ and $p=0.002$). In the not-seizure free group, we did not find this difference in SOZ and non-SOZ ($p=0.67$), but we observed a lower indegree in RA compared to non-RA ($p=0.006$).

Outdegree (Figure 3 B)

In three patients (3, 9, 12), the outdegree was higher for nodes in the SOZ (data not shown). These patients were all seizure free after surgery. In seven patients (2, 3, 4, 9, 12, 13, 16), the outdegree was higher for nodes in the RA. Six of these patients (all except 13) were seizure free after surgery. At group level, the outdegree was higher in both the SOZ ($p<0.001$) and RA ($p<0.001$).

When we compared the seizure free patients with the not-seizure free patients (Figure 5 A), the outdegree was higher in the RA and SOZ compared to non-epileptogenic tissue in seizure free patients (respectively, $p<0.001$ and $p=0.004$). Remarkably, the outdegree was also higher in the SOZ compared to non-SOZ in not-seizure free patients ($p=0.02$).

Betweenness centrality (Figure 3 C)

In patient 6, we found a higher betweenness centrality for the nodes in the SOZ. In patient 3, 12, the betweenness centrality was higher in nodes in the RA. In patient 10, the betweenness centrality was higher in non-RA nodes. At group level, we did not observe any differences. In seizure free patients (Figure 5 A), we saw a trend towards significant lower betweenness centrality in RA than in non-RA ($p=0.06$). We did not see a difference in not-seizure free patients.

Directionality of connections for each node

Activating connections

In three patients (3, 7, 16), the percentage of activating connections was higher in the RA than in non-RA nodes (Figure 4 A). In two patients (3, 7), the same results were found in SOZ compared to non-SOZ. At group level, a higher percentage of activating connections was found in the RA than in non-RA nodes ($p=0.01$). When comparing seizure free patients with not-seizure free patients, we observed a higher percentage of activating connections in the RA than in non-RA nodes in not-seizure free patients ($p=0.001$) (Figure 5 B). A similar trend was observed in SOZ nodes in not-seizure free patients ($p=0.06$).

Bidirectional connections

In one patient (13), the percentage of bidirectional connections was higher in the RA than in non-RA nodes (Figure 4 B). A similar trend ($p<0.1$) was found in six other patients (2, 4, 5, 9, 12, 18). In one patient (7), a lower percentage of bidirectional connections was found in both the RA and SOZ nodes compared to non-epileptogenic nodes. At group level, no difference was found between the epileptogenic and non-epileptogenic nodes. The percentage of bidirectional connections was lower in the RA in not-seizure free patients ($p=0.03$) and higher in the RA in seizure free patients ($p=0.04$) (Figure 5 B).

Receiving connections

In three patients (3, 13, 16), the percentage of receiving connections was lower in the RA than in non-RA nodes (Figure 4 C). In patient 3, this was also found for the SOZ compared to non-SOZ. At group level, the same result was observed for the RA ($p=0.01$). In seizure free patients, a lower percentage of receiving connections was observed in the RA compared to non-RA nodes ($p=0.05$) (Figure 5 B). A similar trend was observed in RA nodes in not-seizure free patients ($p=0.10$).

The destination of connections from in and outside epileptogenic tissue

In all but two patients (11, 13), the ratio of non-RA nodes with connections to non-RA nodes was higher than to RA nodes. In all but three patients (6, 11, 13), the ratio of RA nodes with connections to RA nodes was higher than to non-RA nodes. The same results were visible in most of the patients when analyzing SOZ nodes, when analyzing at group level, or when analyzing seizure free and non-seizure free patients separated ($p<0.001$) (Figure 5 C).

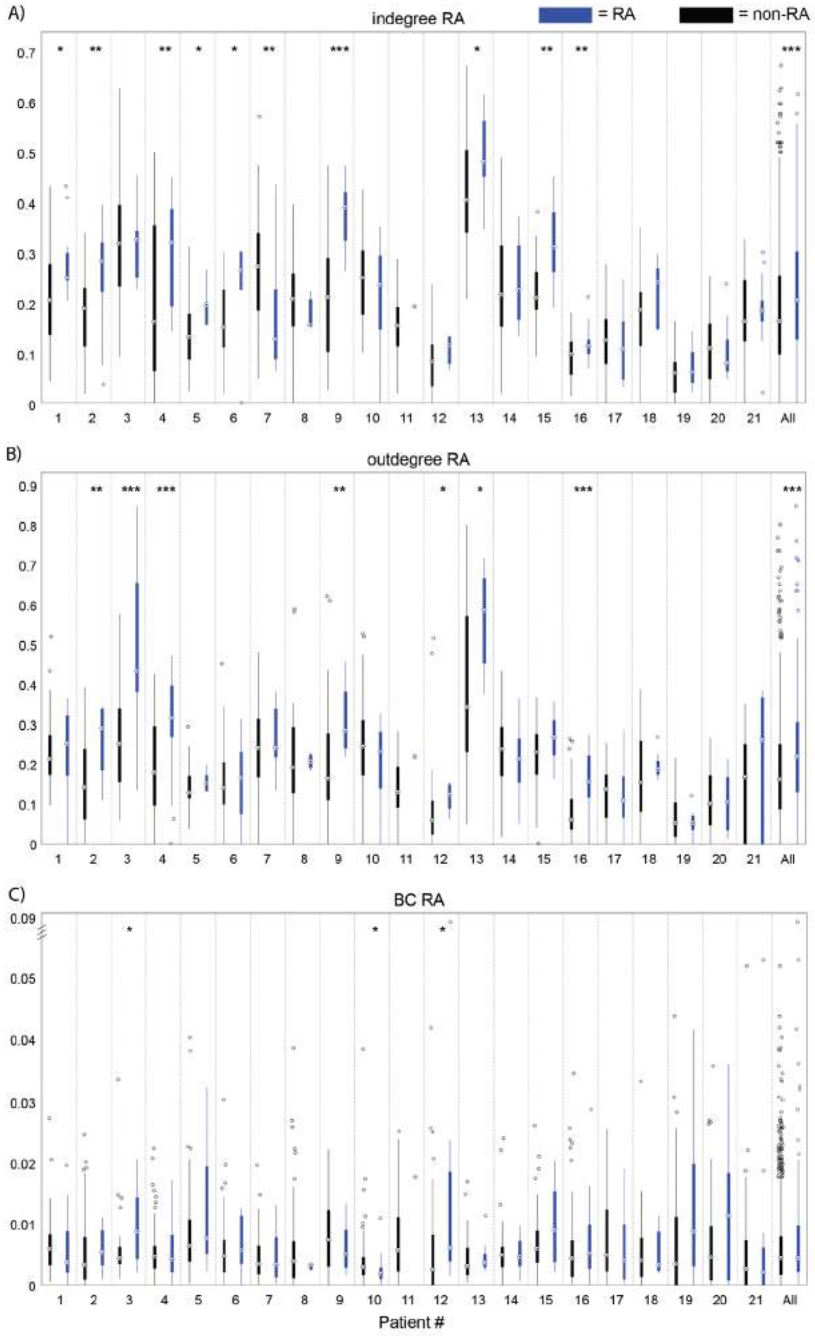

*Figure 3: A) The indegree in RA (blue) and in non-RA (black); B) The outdegree in RA (blue) in non-RA (black); C) The betweenness centrality in RA (blue) and in non-RA (black). Note that the y-axis is broken to facilitate visibility of the low and wide distribution of BC-values. *=p<0.05, **=p<0.01, ***=p<0.001*

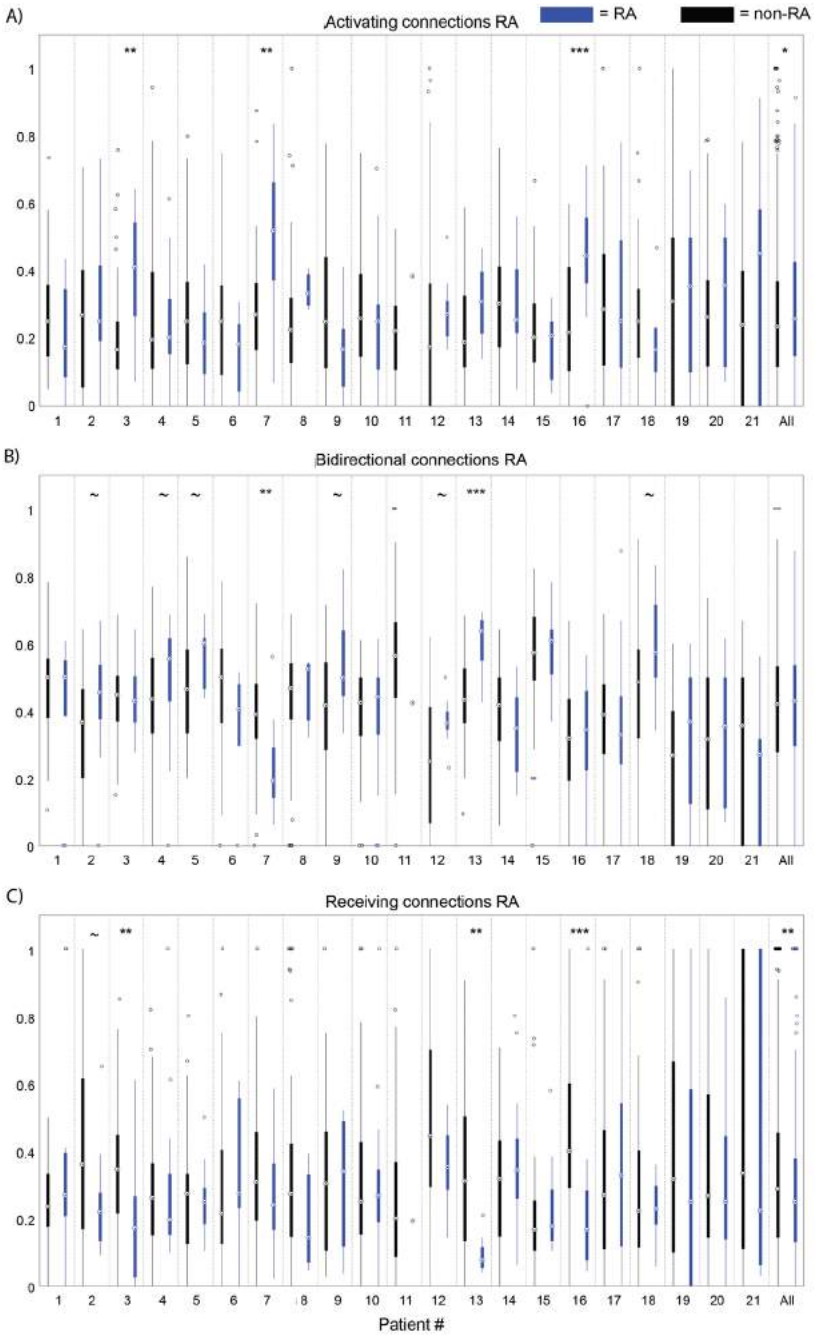

*Figure 4: A) Ratio of activating connections of all connections involving each node in the RA (blue) and non-RA (black); B) Ratio of bidirectional connections of all connections involving each node in the RA (blue) and non-RA (black); C) Ratio of receiving connections of all connections involving each node in the RA (blue) and non-RA (black). ~=p<0.1, * =p<0.05, **=p<0.01, ***=p<0.001*

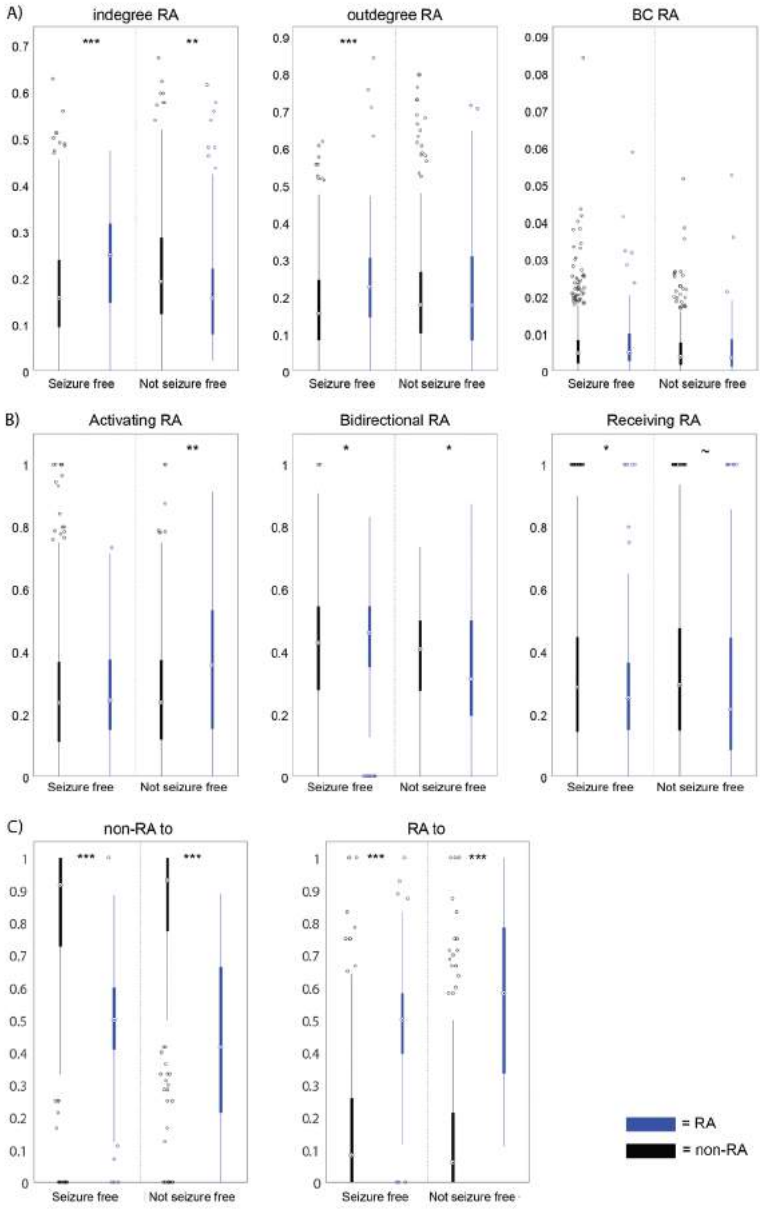

Figure 5: A) The indegree, outdegree, and betweenness centrality in the RA (blue) and non-RA (black) in seizure free and not-seizure free patients; B) Ratio of Activating, Bidirectional and Receiving connections of all connections involving each node in the RA (blue) or non-RA (black) for seizure free patients and not-seizure free patients; C) Ratio of connections from (non-)RA nodes to (non-)RA nodes in both seizure free and not-seizure free patients. In both seizure free and not-seizure free patients, the ratio of connections from non-RA nodes to non-RA nodes is higher than to RA nodes. The ratio of RA nodes to RA nodes is higher than to non-RA nodes. ~=p<0.1, =p<0.05, **=p<0.01, ***=p<0.001*

Discussion

Main findings

The in- and outdegree were higher for nodes within epileptogenic tissue (SOZ and RA) in individual patients at group level, and more so in seizure free patients. In not-seizure free patients, the indegree was lower in the RA-nodes. These results are summarized in Figure 6. In four patients (patient 2, 6, 15, 16), the node with the highest indegree was located in the RA. In patient 20, the node with the highest indegree was located in the SOZ. This node was not resected during surgery and the patient was not-seizure free after surgery. In none of the patients, the node with the highest outdegree or betweenness centrality was located in the SOZ/RA.

Remarkably, patient 13, who did not become seizure free, also showed similar results for in- and outdegree as other patients. This patient had a resection in the pericentral motor mouth area. Some tissue involved in seizure onset was not removed since the motor hand function was located there. After surgery, seizures changed to an onset with twitches in the hand. Since part of the tissue involved in seizure onset was resected, this might explain the high in- and outdegree in the epileptogenic tissue, although this patient was not seizure free after surgery. Furthermore, the difference in ratio between non-RA nodes to (non-)RA nodes and the difference in ratio between RA nodes to (non-)RA was not significant, suggesting that the RA should have been larger to render this patient seizure free.

At group level, and when comparing seizure free and not-seizure free patients, no difference was found in betweenness centrality inside or outside epileptogenic tissue.

The percentage of activating connections was higher in RA nodes in a few patients individually, at group level, and in not-seizure free patients. In a few patients individually, at group level, and in seizure free patients, the percentage of bidirectional connections was higher in RA nodes. In a few patients individually, at group level and in seizure free patients, the percentage of receiving connections was lower in the RA nodes.

In most patients individually, at group level, and when comparing seizure free and not seizure free patients, the percentage of non-RA nodes to non-RA nodes was higher than non-RA nodes to RA nodes and the percentage of RA nodes to RA nodes was higher than RA nodes to non-RA nodes.

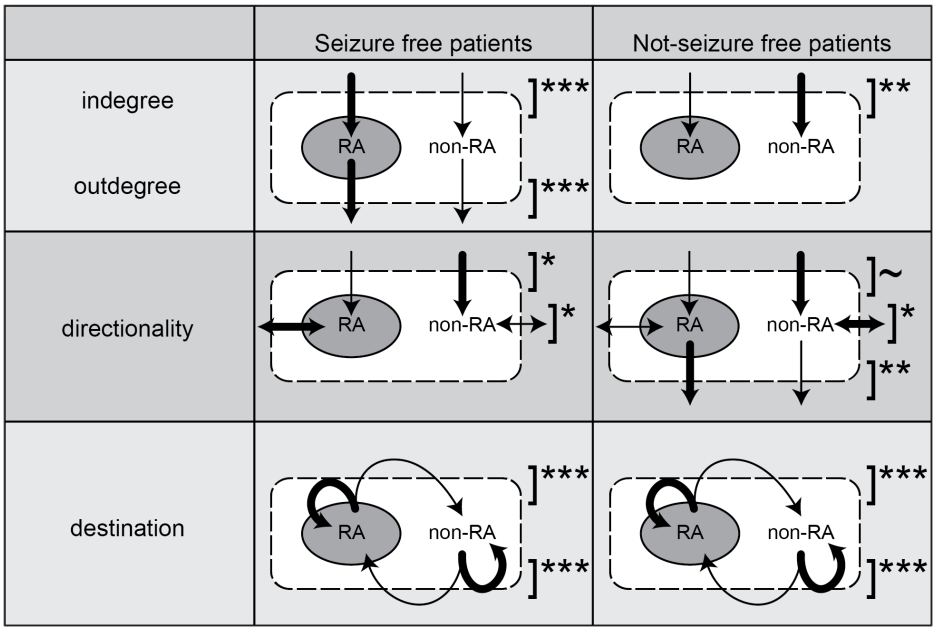

Figure 6: Summary of findings. *A) Indegree and outdegree in seizure free and not-seizure free patients: The indegree was increased (displayed with a thick arrow towards the RA) in RA-nodes compared to non-RA nodes (displayed with a thin arrow towards the non-RA) in seizure free patients. The opposite was found when comparing RA-nodes with non-RA nodes in not-seizure free patients. The outdegree was increased (displayed with a thick arrow originating from the RA) in RA-nodes compared to non-RA nodes (displayed with a thin arrow originating from the non-RA) in seizure free patients. No difference in outdegree was observed in not-seizure free patients. B) The directionality of connections in seizure free and not-seizure free patients: The percentage of receiving connections (arrows towards the (non-) RA-areas) was decreased in RA-nodes compared to non-RA-nodes in both seizure free and not-seizure free patients. The percentage of bidirectional connections (arrows on both sides) was increased in the RA-nodes compared to non-RA nodes in seizure free patients. The opposite was found in not-seizure free patients. The percentage of activating connections (arrows pointing from the (non-RA)-areas) was increased in RA-nodes in not-seizure free patients. No difference in percentage of activating connections was observed in seizure-free patients. C) The destination of connections from the RA or non-RA nodes: In both seizure free and not-seizure free patients, the ratio of connections from RA to RA-nodes and non-RA to non-RA nodes was higher, suggesting an isolated epileptogenic area. NS = not significant, ~= p<0.1,*=p<0.05, **=p<0.01, *** =p<0.001.*

Implications

We found a high indegree and outdegree in epileptogenic tissue. This is consistent with Mouthaan et al. [54], who found a high count of ERs in the SOZ, which can be interpreted as a high indegree. Boido et al. [71] reported that the epileptogenic zone can be identified by mapping bidirectionality features of ERs. A larger percentage of bidirectional and a lower percentage of receiving connections was observed in epileptogenic tissue (both RA/SOZ), as compared to non-epileptogenic tissue. Hebbink et al. [67] suggested a node that is driving the seizures is characterized by many connections originating from such a region, and only a few connections towards this region. Removal of this area may have a positive effect on seizure rate.

RA nodes had more connections to RA nodes than to non-RA nodes, and non-RA nodes had more connections to non-RA nodes than to RA nodes. This result suggests that the RA is densely connected and that connections from non-RA to RA are sparser.

In a recent review, Matsumoto et al. [73] suggested that the amplitude of the ERs in epileptogenic and 'normal' tissue is higher when stimuli are applied to the seizure onset zone [51], but the distribution of these ERs is not adapted in the epileptogenic network. In this study, we did not investigate the amplitude of an ER, but we found specific network properties of epileptogenic tissue.

Other research on functional networks

Most research on functional networks has focused on the ictal phase, or on the transition from the interictal to ictal phase. Several studies found highly interconnected nodes within epileptic networks in ictal scalp EEG [68], [59], nodes with highest outdegree in the RA in ictal SEEG [57], or nodes with highest in- and outdegree in the SOZ in patients with a good outcome [74], [75]. Khambhati et al. [76] concluded that connections within the SOZ are the strongest. These studies describe the epileptogenic tissue as highly interconnected, resulting in high in- and outdegree. This is in agreement with our findings of high in- and outdegree in the epileptogenic tissue.

We did not find betweenness centrality an indicator of epileptogenic tissue. Other studies only reported an increase in the betweenness centrality in the gamma band [77], [70], or in a few seconds prior to seizure onset [75]. Geier et al. [78] found that the betweenness centrality in pre-ictal ECoG (using cross-correlation) was highest in brain regions neighboring the SOZ. This idea is supported by results for one of our patients, see the example in (Figure 7). For this patient, it is possible that a high in- and outdegree in the SOZ led to a highly interconnected SOZ with only a small number of connections outside epileptogenic tissue.

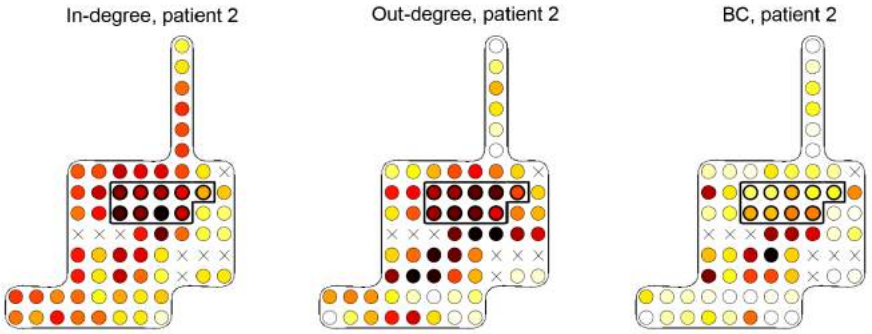

Figure 7: The indegree (left), outdegree (middle), and betweenness centrality (right) in patient 2. The RA is enclosed by a thicker line. (white = low, yellow = average, dark red = high) The indegree is high in the RA. There is a broad stripe of electrodes with a high outdegree including the RA. Electrodes below the RA have a relatively high BC. X=electrodes excluded from analysis since these were not stimulated during SPES.

Limitations

In this study, we used ECoG data, in which spatial sampling of the brain is limited to the location suspected of seizure onset and adjacent functional areas. Therefore, we are not able to extend our findings to large scale brain networks and to assert if a relationship between two nodes is direct, or indirect with an un-sampled node in between. Furthermore, electrodes on the boundary of the grid might have shown fewer connections, since not all areas around them were sampled. We corrected for this by considering the number of stimulations in each electrode.

Another bias might have been that often the grids are placed in such a way that the presumed SOZ is located in the middle of the grid. This could have led to a higher in- and outdegree since all areas around the grid-centers are sampled. As it turned out, in 11 patients the SOZ/RA was actually located on a grid border, or on a strip with no sampled areas around the strip and in respectively 3 and 4 of these patients, the obvious differences in in- and outdegree were still observed. We also calculated an average indegree and outdegree for electrodes on edges, corners, strips, or middle of grids in 21 patients. When correcting for the mean number of connections in an electrode on a specific location, our results did not change.

There was some discrepancy between the RA and the SOZ. The clinically reported RA was larger than the clinically annotated SOZ in most patients. This was often due to anatomical lesions which were visible on MRI, and therefore resected even if outside the SOZ.

Similarly, in patients who continued to experience seizures after surgery, the RA may not have included all of the SOZ, and therefore this might have affected our analysis.

The timing of SPES after implantation of the electrode grids varied among patients but was always at least one day after implantation, diminishing the possible effect of general anesthesia on network excitability.

A disadvantage of SPES is that, although we evoke ERs during an interictal period, it is not clear how our effective network relates to interictal functional networks, or whether it is more similar to an ictal functional network. Future research investigating functional and effective networks in the same patient could give insight into this matter.

Future perspective

We found a high in- and outdegree, a higher percentage of bidirectional connections, and a lower percentage of receiving connections in epileptogenic tissue, suggesting that the epileptogenic tissue is densely connected with itself. These characteristics suggest that analysis of ERs from SPES might indicate the location of epileptogenic tissue. Future studies should focus on analysis of ERs from SPES to localize epileptogenic tissue prospectively.

Conclusion

With this study, we have shown that differences in network properties between epileptogenic and normal tissue exist and may be found using effective SPES networks.

THE EFFECT OF PROPOFOL ON EFFECTIVE BRAIN NETWORKS

The effect of propofol on effective brain networks

D. van Blooijs, S. Blok, G.J.M. Huiskamp, P. van Eijsden, H.G.E. Meijer, F.S.S. Leijten

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Abstract

Objective: We compared the effective networks derived from Single Pulse Electrical Stimulation (SPES) in intracranial electrocorticography (ECoG) of awake epilepsy patients and while under general propofol-anesthesia to investigate the effect of propofol on these brain networks.

Methods: We included nine patients who underwent ECoG for epilepsy surgery evaluation. We performed SPES when the patient was awake (SPES-clinical) and repeated this under propofol-anesthesia during the surgery in which the ECoG grids were removed (SPES-propofol). We detected the cortico-cortical evoked potentials (CCEPs) with an automatic detector. We constructed two effective networks derived from SPES-clinical and SPES-propofol. We compared three network measures (indegree, outdegree and betweenness centrality), the N1-peak-latency and amplitude of CCEPs between the two effective networks.

Results: Fewer CCEPs were observed during SPES-propofol (median: 6.0, range: 0-29) compared to SPES-clinical (median: 10.0, range: 0-36). We found a significant correlation for the indegree, outdegree and betweenness centrality between SPES-clinical and SPES-propofol (respectively r_s=0.77, r_s=0.70, r_s=0.55, $p<0.001$). The median N1-peak-latency increased from 22.0 ms during SPES-clinical to 26.4 ms during SPES-propofol.

Conclusions: Our findings suggest that the number of effective network connections decreases, but network measures are only marginally affected.

Significance: The primary network topology is preserved under propofol.

Introduction

Propofol is an intravenous agent used for induction and maintenance of general anesthesia during surgery and in the intensive care unit. Propofol inhibits, among other mechanisms of action, the γ-aminobutyric acid ($GABA_A$)-receptor by slowing the channel closing time of the receptor, with an inhibitory effect on neurotransmission [79–82]. In the EEG, slowing of brain signals and reduction of epileptic activity is observed [83–85], as well as suppression of motor evoked potentials in a dose-dependent manner [86].

Analyzing the difference between brain networks while awake or while under anesthesia may give us additional and complementary insight in the effects of anesthesia at a network level. Brain networks can be categorized as structural, functional or effective networks [40]. Structural networks are based on the anatomical connections between brain regions (typically corresponding to white matter fiber tracts). Functional networks are based on the temporal dependency between neural activities of different brain regions, usually estimated in fMRI or (intracranial) EEG data. Analysis of functional brain networks in human subjects has informed us that there is a balance between local segregation and global integration in the awake state, which means that lower-level information can be processed locally and modularly, whereas higher-level information is distributed efficiently over the brain because of global integration [87]. This balance between local segregation and global integration is disturbed in anesthesia-induced loss of responsiveness [88].

Effective networks describe the interaction between brain regions caused by perturbation in one brain region that leads to responses in other brain regions [89]. Single Pulse Electrical Stimulation (SPES) is one of the techniques that can be used to study effective brain connectivity by using direct electrical stimulation and recording of intracranial electrodes on the brain [44]. With SPES, we stimulate two adjacent electrodes and analyze the cortico-cortical evoked potentials (CCEPs) in all other electrodes [89]. CCEPs have a sharp negative deflection (N1) that occurs between 9 and 100 ms after the stimulation artefact. A CCEP exposes an effective network connection between the stimulation site and the recording electrode. This has provided insight into eloquent brain networks such as language, cognitive and motor networks [43,44,90].

The complex network structure of the brain can be characterized by a set of topological network measures, such as the indegree, outdegree and betweenness centrality [55,57,70,89,91–93]. The indegree is a measure describing the number of incoming connections towards an electrode of interest. In an effective network, this is the number of CCEPs evoked in the electrode of interest after stimulating other electrode pairs. The outdegree describes the number of outgoing connections from an electrode of interest. In an effective network, this is the number of CCEPs evoked elsewhere after

stimulating the electrode of interest. The betweenness centrality is the fraction of all shortest paths in the network that pass through an electrode of interest [55]. Electrodes with a high betweenness centrality are assumed to be important controllers of a network [94]. These measures characterize the topological network and enable us to compare the network in an awake state to a network under anesthesia.

We analyzed whether propofol alters the effective network connections by investigating the number of CCEPs, the indegree, outdegree, betweenness centrality, the N1-peak-latency and the N1-peak-amplitude. To the best of our knowledge, this is the first study that compares effective brain networks in the same subjects in the awake state and under general propofol-anesthesia.

Materials and methods

Subjects and data recording

Between 2020 and 2022, patients who underwent electrocorticography (ECoG) recordings for epilepsy surgery evaluation were asked to give consent to participate in this study (PRIOS: **P**ropofol **I**ntra-**O**perative **S**PES). The study complied with the Dutch law on Medical Research in Humans and was approved by the medical research ethics committee of the University Medical Centre Utrecht. The ECoG implant strategy was determined solely by clinicians and not influenced by this study. ECoG data was recorded with a sample frequency of 2048 Hz.

Stimulation protocols

We applied two SPES protocols (Figure 1): SPES-clinical and SPES-propofol. SPES-clinical was performed at least one day after subdural electrode grid implantation in the awake subject as part of clinical routine. Ten monophasic electrical pulses (0.2 Hz, 1 ms, 8 mA) were applied to each pair of adjacent electrodes in consecutive numbers across the implanted electrode grid (e.g. 1-2, 2-3, etc., Supplementary Figure 1). We decreased the current intensity to 4 mA when electrodes were located on the pre- or post-central gyrus. After five stimuli, the anode and cathode were switched to reduce the stimulus artefact when averaging the responses to these stimuli.

SPES-propofol was performed under propofol-anesthesia at the start of the grid explantation surgery. We started with SPES-propofol at least five minutes after the initial administration of propofol, during preparations for grid explantation and often epilepsy surgery. We stimulated each adjacent electrode pair twice and switched anode and cathode after the first stimulus. If we finished the protocol in time and surgical preparations were still ongoing, additional stimuli were applied to some stimulus pairs. We considered all stimuli for analysis.

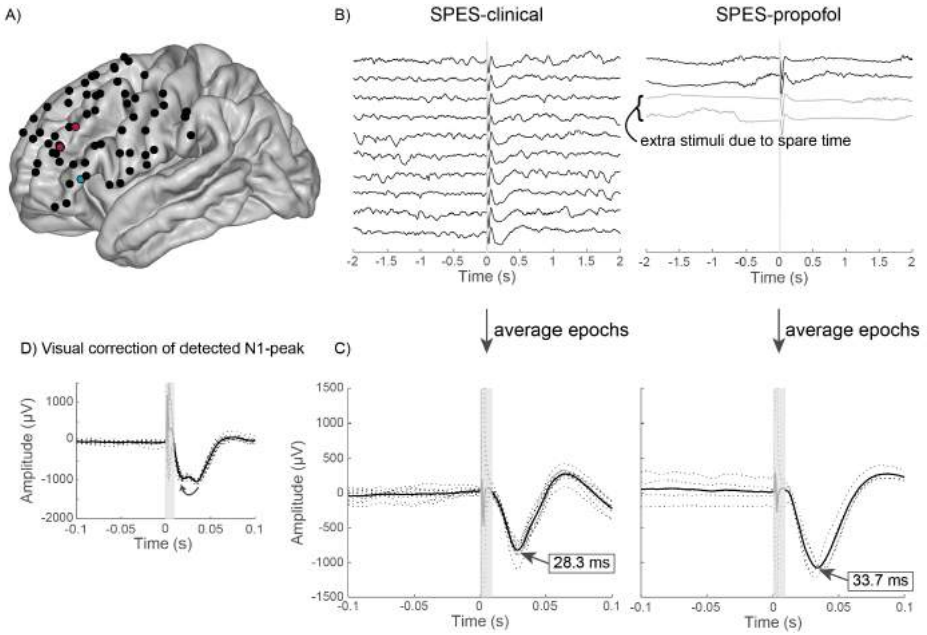

Figure 1: Example of the two SPES (Single Pulse Electrical Stimulation)-protocols in PRIOS03. We performed two SPES protocols: SPES-clinical and SPES-propofol. A) Rendering of a standardized brain with electrode positions of PRIOS03 in MNI305 coordinates. The pink electrodes are stimulated. The responses to these stimuli in the blue electrode are shown in B). B) The responses to stimulation for SPES-clinical (left) and SPES-propofol (right). We were able to apply four stimuli to this stimulus pair during SPES-propofol due to spare time and visualized the four responses to these stimuli. C) We averaged the ten (in SPES-clinical) and four (in SPES-propofol) responses to stimuli visualized in B. The individual responses are displayed with dotted lines, the averaged response is displayed with a continuous line. The grey area corresponds to the interval in which no physiological response could be measured due to the stimulation artefact. The peak at 28.3 ms and 33.7 ms was the latency of the N1-peak of the CCEP (cortico-cortical evoked potential). D) Example of visual correction. When two small peaks were visible during the N1-waveform, the first N1-peak was selected in the averaged CCEP response.

Signal processing

A clinical neurophysiologist (FL) annotated periods with burst suppression during SPES-propofol. We excluded epochs that were recorded during burst suppression, because CCEPs are suppressed during burst suppression [95].

We excluded data from noisy electrodes, and electrodes located on top of other electrode grids. ECoG recordings were converted to the Brain Imaging Data Structure [96]. For each electrode, epochs with a time window of 2 s pre-stimulus to 2 s post-stimulus, time-locked to the stimulus artefact, were re-referenced by subtracting the averaged signal of 10% of the electrodes with the lowest variance

post-stimulation (Figure 1B). For each electrode, epochs of all stimuli per stimulus pair were averaged (Figure 1C).

N1-peaks detection and visual check

The standard deviation (SD) was calculated in the pre-stimulus window (-2 s to -0.1 s). N1-peaks were detected [89] in each averaged epoch per electrode when the evoked response exceeded 2.6 * SD (Figure 1C). The detected N1-peaks of the CCEPs were visually checked by two observers (DvB and SB). When an incorrect N1-peak was selected by the detector, the correct N1-peak was selected manually.

For each subject and each SPES-protocol, an inter-observer agreement was calculated between the two observers with the unweighted Cohen's kappa. Subjects were excluded from further analyses when the inter-observer agreement of SPES-clinical or SPES-propofol was lower than 0.6. We only included N1-peaks for further analyses when these were visually confirmed by both observers. When both observers selected N1-peaks with more than five samples difference, these N1-peaks were visually checked (SB), and the correct N1-peak was selected (Figure 1D). N1-peaks less than five samples apart were averaged.

Analysis

We first analyzed with a chi-square test whether stimulation of a given electrode pair would evoke a CCEP in similar electrodes in both SPES-protocols. We then used the Wilcoxon Signed Rank-test to compare the number of evoked CCEPs for each stimulus pair between SPES-clinical and SPES-propofol.

For the analysis of the network measures, we defined the electrodes as nodes and therefore, we needed to make the assumption that when stimulation in a stimulus pair would evoke a CCEP in another electrode, both electrodes in this stimulus pair contributed to this evoked CCEP. From this assumption, it follows that we include a connection in the network from both stimulation electrodes to the response electrode. For each electrode, we calculated the indegree, outdegree and betweenness centrality during SPES-clinical and SPES-propofol. We normalized these network measures by considering the number of possible connections (given the number of grid electrodes that was implanted) to enable comparison between subjects [89]. We used the Spearman rank correlation to correlate the indegree, outdegree and betweenness centrality between SPES-clinical and SPES-propofol.

For the analysis of the differences in N1-peak-latencies and N1-peak-amplitudes, we only included the N1-peak-latencies and amplitudes of CCEPs that were present during both SPES-clinical and SPES-propofol. We used the Wilcoxon Signed Rank-

test to compare the N1-peak-latency and amplitude of the CCEPs evoked during SPES-clinical and SPES-propofol. All statistical analyses were corrected for multiple testing with FDR correction ($p<0.05$).

Code and data availability

We performed all analyses and generated all figures using Matlab R2022b. The code is available on https://github.com/UMCU-EpiLAB/umcuEpi_PRIOS. The data is available on https://openneuro.org/datasets/ds004370.

Results

Patient characteristics

We included nine subjects (four females) with a median age of 27 years (range 13 – 53 years) (Table 1). All subjects were fully informed of the nature of this study and gave informed consent. The electrode grids and strips consisted of platinum circular electrodes embedded in silicone with a 4.2 mm^2 contact surface and an inter-electrode distance of 1 cm (Ad-Tech, Racine, WI). PRIOS01 and PRIOS09 had an additional depth-lead with 6 electrodes implanted in the presumed epileptogenic region (DIXI Medical, Chaudefontaine, Marne, France).

Table 1: Characteristics of subjects included in the PRIOS study. Subjects shaded in grey were excluded from further analysis. M = male, F = female, NA = not applicable, SPES-clinical = Single Pulse Electrical Stimulation protocol after subdural electrode grid implantation in the awake subject as part of clinical routine, SPES-propofol = Single Pulse Electrical Stimulation protocol performed under propofol-anesthesia at the start of the grid explantation surgery.

Subject	Age (years)	Sex	Location of grid	Number of implanted electrodes / stimulus pairs	Cohen's Kappa SPES-clinical	Cohen's Kappa SPES-propofol
PRIOS01	22	M	Left, temporal	48 / 35	0.74	0.80
PRIOS02	53	F	Left, fronto-temporal	80 / 54	0.72	0.76
PRIOS03	37	M	Left, frontal	64 / 52	0.86	0.88
PRIOS04	24	M	Left, frontal, interhemispheric, parietal	56 / 48	0.76	0.61
PRIOS05	51	F	Right, pre-and post-central gyrus, interhemispheric	64 / 53	0.74	0.72
PRIOS06	13	F	Right, pre- and post-central gyrus, parietal		0.30	0.47
PRIOS07	44	M	Left, fronto-temporal, interhemispheric		NA	NA
PRIOS08	15	F	Left, temporo-occipital		NA	NA
PRIOS09	27	M	Left, temporal	56 / 44	0.89	0.81

Two subjects (PRIOS07 and PRIOS08) were excluded, because we were not able to perform SPES-propofol due to technical problems. One subject (PRIOS06) was excluded from further analysis because the interobserver agreement was lower than 0.6 (Table 1).

Numbers of evoked CCEPs

In all subjects, we found a large overlap in the electrodes in which a CCEP was evoked after stimulating a stimulus pair in both SPES-protocols (Figure 2). Only a small number of electrodes showed a CCEP after stimulating a stimulus pair during SPES-propofol that did not show a CCEP after stimulating the same stimulus pair during SPES-clinical. There are a number of electrodes in which a CCEP was evoked during SPES-clinical without a correlate in SPES-propofol. In all subjects, we found that fewer CCEPs were evoked during SPES-propofol compared to SPES-clinical (Figure 3). Figure 3 also shows that in most stimulus pairs, the relative number of evoked CCEPs, and therefore the ranking, remained the same under anesthesia.

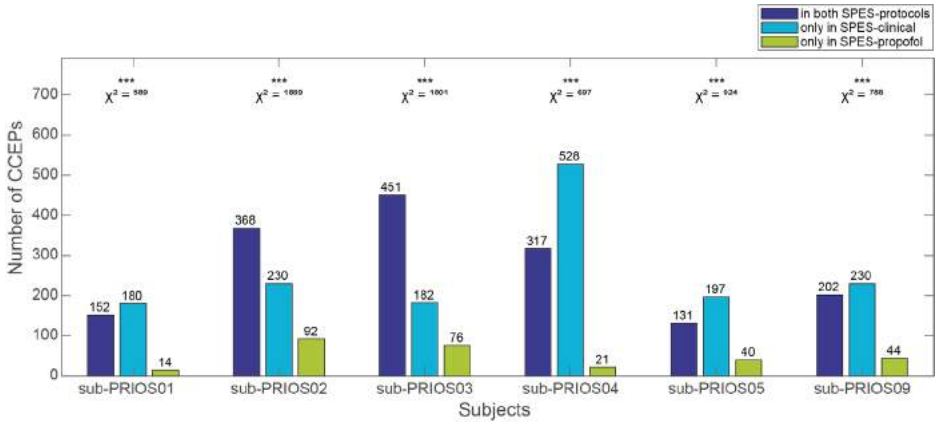

*Figure 2: Schematic overview of the number of cortico-cortical evoked potentials (CCEPs) evoked during the two SPES (Single Pulse Electrical Stimulation)-protocols. For each subject, the numbers of evoked CCEPs are displayed in both SPES-clinical and SPES-propofol (purple), only during SPES-clinical (blue) and only during SPES-propofol (green). In all subjects, there is a high association between SPES-clinical and SPES-propofol which means that when a CCEP was evoked after stimulating a certain stimulus pair in one of the SPES-protocols, it would be evoked after stimulating a certain stimulus pair in the other SPES-protocol as well. *** = p<0.001, FDR corrected.*

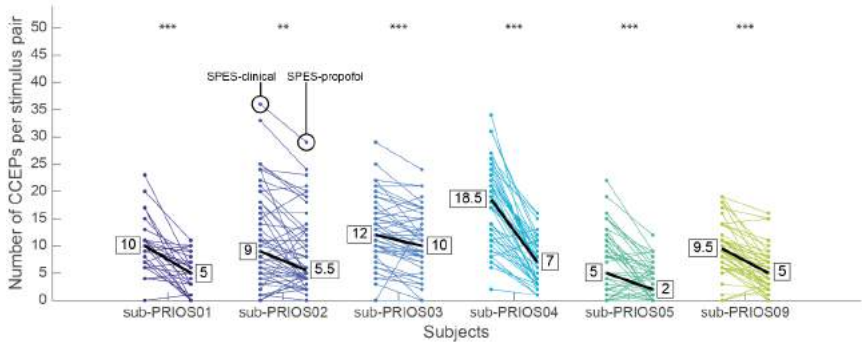

*Figure 3: The number of cortico-cortical evoked potentials (CCEPs) evoked per stimulus pair. Each dot represents the number of CCEPs in one stimulus pair. The left dots represent the numbers of CCEPs evoked during SPES-clinical (Single Pulse Electrical Stimulation protocol after subdural electrode grid implantation in the awake subject as part of clinical routine). The right dots represent the numbers of CCEPs evoked during SPES-propofol (Single Pulse Electrical Stimulation protocol performed under propofol-anesthesia at the start of the grid explantation surgery). Dots of the same stimulus pair are connected by a line to visualize the differences in numbers of evoked CCEPs between the two SPES protocols. The median number of CCEPs evoked per stimulus pair are visualized with the numbers in the boxes and connected with a black line. ** = p<0.01, *** = p<0.001, FDR corrected.*

Network measures: indegree, outdegree and betweenness centrality

The indegree, outdegree and betweenness centrality showed high correlation strengths (Spearman's correlation, $r_s > 0.5$) between SPES-clinical and SPES-propofol (Figure 4). All network measures showed around twice as high values for all electrodes during SPES-clinical compared to the values during SPES-propofol.

N1-peak-latencies and amplitudes

When we analyzed N1-peak-latencies in each individual subject, we found an increase in N1-peak-latency in SPES-propofol in three subjects (PRIOS02, PRIOS03 and PRIOS04: respectively 29.3 ms → 32.2 ms, 22.0 ms → 26.9 ms, 12.7 ms → 13.2 ms) (Figure 5 A-B). We found a decrease in N1-peak-latency in one subject (PRIOS09: 35.6 ms → 31.2 ms). When combining all N1-peaks of all subjects, the N1-peak-latency increased from 22.0 ms during SPES-clinical to 26.4 ms during SPES-propofol.

When analyzing the N1-peak-amplitudes in each individual subject, we found a more negative N1-peak-amplitude in SPES-propofol in two subjects (PRIOS02, PRIOS03: respectively -392 μV → -399 μV, -592 μV -701 μV) and a less negative N1-peak-amplitude in three subjects (PRIOS01, PRIOS04, PRIOS05: respectively -424 μV → -312 μV, -822 μV → -535 μV, -421 μV → -349 μV) (Figure 5C). When combining all N1-peaks of all subjects, the N1-peak-amplitude was less negative during SPES-propofol (-499 μV → -466 μV).

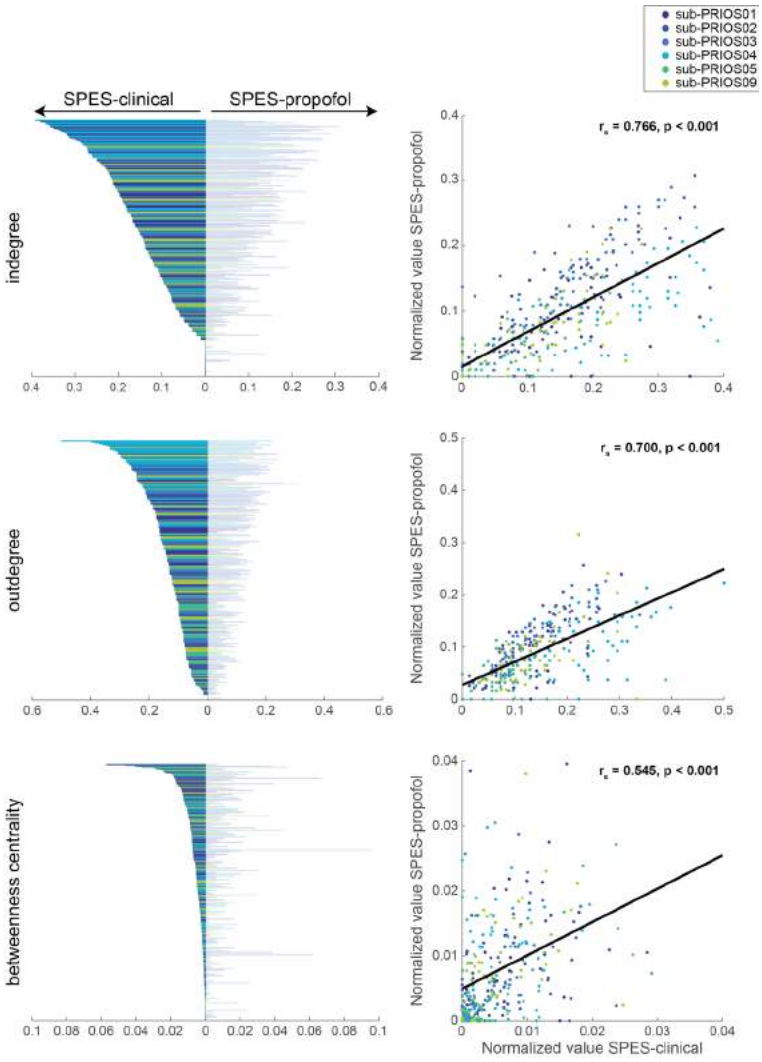

Figure 4: Correlation of the indegree, outdegree and betweenness centrality between the two SPES (Single Pulse Electrical Stimulation)-protocols. On the left: horizontal bars of all subjects combined for the indegree (upper), outdegree (middle) and betweenness centrality (lower). Each horizontal bar represents the normalized value of a network measure per electrode. The values of the network measures of SPES-clinical are sorted in descending order (SPES-protocol after subdural electrode grid implantation in the awake subject as part of clinical routine, on the left side of the bar plot). The values of network measures during SPES-propofol (SPES-protocol performed under propofol-anesthesia at the start of the grid explantation surgery, on the right side of the bar plot) are sorted accordingly. On the right: scatter plots are displayed for the network measures indegree (upper), outdegree (middle) and betweenness centrality (lower). All three network characteristics showed significant correlations between SPES-clinical and SPES-propofol (Spearman's correlation, $p<0.001$, FDR corrected). The strength of the correlation was expressed with the correlation coefficient (r_s). Both the horizontal bars and dots in the scatter plots have different colors for all individual subjects.

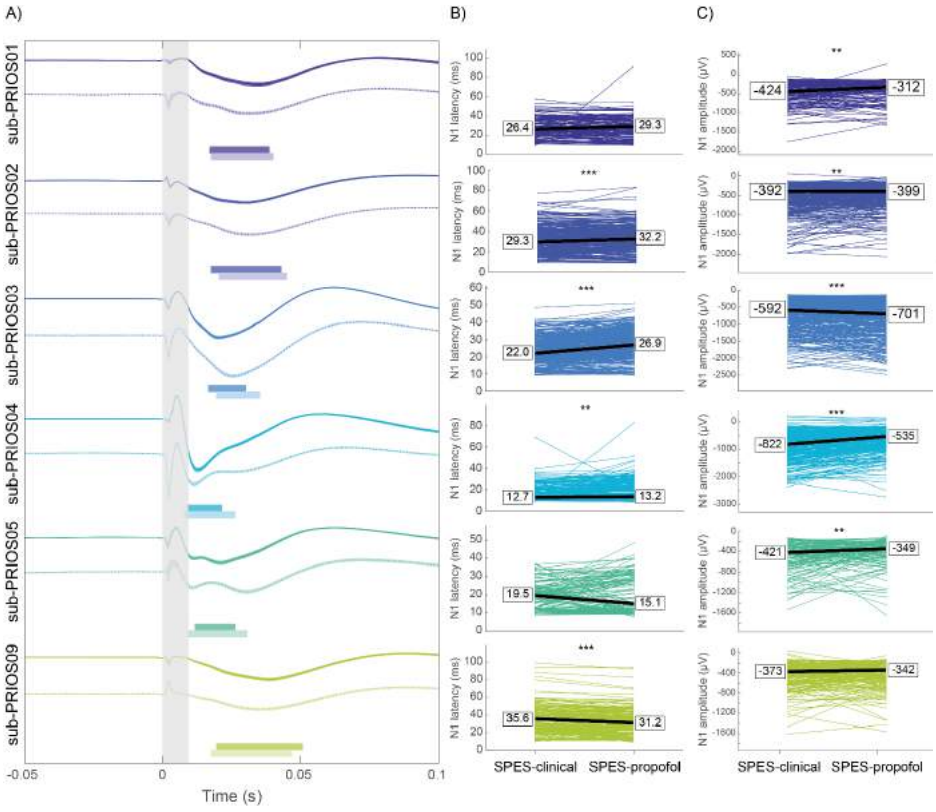

*Figure 5: Overview of the averaged cortico-cortical evoked potentials (CCEPs) for both SPES (Single Pulse Electrical Stimulation)-protocols. A) Six sets of CCEP-plots: the averaged CCEP ± Standard Error of the Mean (SEM) during SPES-clinical (SPES-protocol after subdural electrode grid implantation in the awake subject as part of clinical routine, upper) and during SPES-propofol (SPES-protocol performed under propofol-anesthesia at the start of the grid explantation surgery, lower) for each individual subject. Below each set of CCEP-plots, two horizontal bars are shown, indicating the mean ± SEM of the N1-peak-latencies in SPES-clinical (upper) and SPES-propofol (lower). B) The median latency of each N1-peak during SPES-clinical and SPES-propofol are represented by dots and connected by a line to indicate how the latency changes between the two protocols. The median latency is displayed by a thicker black line and the median values are displayed in boxes. C) The median amplitude of each N1-peak during SPES-clinical and SPES-propofol are represented by dots and connected by a line to indicate how the amplitude changes between the two protocols. The median amplitude is displayed by a thicker black line and the median values are displayed in boxes. ** = p<0.01, *** = p<0.001, FDR corrected.*

Discussion

We studied whether the effective network derived from SPES-clinical was altered due to propofol. We found a large overlap between the electrodes in which a CCEP was evoked during SPES-clinical and SPES-propofol. The number of evoked CCEPs during SPES-propofol was lower than the number of evoked CCEPs during

SPES-clinical. This decrease might be caused by the inhibitory effect of propofol on neurotransmission [79–82]. Although the lower number of evoked CCEPs during SPES-propofol could result in an altered network topology because of missing connections, the ranking of electrodes for values of network measures (indegree, outdegree, betweenness centrality) did not change: e.g. an electrode with a high indegree during SPES-clinical also had a high indegree during SPES-propofol. This means that the topology of the effective network was not altered during SPES-propofol. This was supported by the observation that the stimulus pair with the highest number of evoked CCEPs was the same for both SPES-clinical and SPES-propofol in two subjects (PRIOS02 and PRIOS03) (Supplementary Figure 3 and Supplementary table 1). In three subjects (PRIOS01, PRIOS04, PRIOS05), the location of the stimulus pair with the highest number of evoked CCEPs during SPES-propofol was localized near the stimulus pair with the highest number of evoked CCEPs during SPES-clinical. Furthermore, we observed that the electrode with maximal N1-peak-amplitude was the same for both SPES-clinical and SPES-propofol in nine situations or these electrodes were located next to each other in three situations (Supplementary appendix and Supplementary Figure 4). This was in agreement with a study [97] in which they compared the location of the maximal N1-peak-amplitude in the awake state and under general anesthesia in the dorsal language white matter pathway. Interestingly, other studies show that activity of brain areas within a network becomes more independent from one another and the exchange and distribution of information are reduced during deep sedation [98,99]. Moreover, the number of local connections was significantly decreased during anesthesia [99]. The latter is in agreement with our findings. With ECoG, we only sample a part of the brain, which might give an explanation why we only found a decrease in the number of connections during SPES-propofol and no changes in network topology.

Median N1-peak-latency during SPES-propofol (26.4 ms) increased by 4.4 ms compared to SPES-clinical (22.0 ms). PRIOS09 showed the opposite effect: N1-peak-latency decreased during SPES-propofol. This difference in change in latency might be due to heterogeneity in underlying pathologies or might also be influenced by the fact that the subjects included in this study used various anti-seizure medication to suppress seizure activity. The timing of N1-peak-latencies is in agreement with several other studies. In awake patients, an N1-peak-latency of 27.9 ms (range 22-36 ms) was found in the arcuate fasciculus [44]. Under general anesthesia, an N1-peak-latency of 23 ± 3 ms [100] and during awake craniotomy, an N1-peak-latency of 28 ± 4 ms [101] was found. Although all N1-peak-latencies were measured in the arcuate fasciculus, it is difficult to compare these N1-peak-

latencies from different subjects across these studies, since age, and probably other factors, might affect N1-peak-latencies [102]. A study that compared the N1-peak-latency in the arcuate fasciculus within subjects both under general anesthesia and during awake craniotomy found N1-peak-latencies of 26.6 ± 9.1 ms under general anesthesia and 23.2 ± 8.3 ms in the awake state [95]. These N1-peak-latencies are comparable to the N1-peak-latencies we found in this study with four subjects who had coverage of the frontal and temporal endpoints of the arcuate fasciculus [103] by subdural electrodes (Supplementary Figure 2).

N1-peak-amplitudes were more negative in two subjects, and less negative in three subjects during SPES-propofol. This indicates that there was no clear effect of propofol on N1-peak-amplitude. Yamao et al. [97] concluded that the N1-peak-amplitude had a tendency to increase in the awake state when investigating the dorsal language white matter pathway. Differences with our findings might be caused by the significant effect of number of trials on N1-peak-amplitude (Supplementary Figure 5).

Unique in our study is that we applied SPES in all electrodes and not only in electrodes located on the endpoints of the arcuate fasciculus to analyze the effect of propofol on effective networks in general. We took as gold standard the awake state at least one day after surgery (SPES-clinical), ensuring that the effect of propofol and other anesthesia used during implantation surgery have been eliminated.

One of the limitations of this study is the small number of participants (n = 6). With more included subjects, differences in effective connectivity across cortical regions could be investigated. Other studies found the most prominent changes in functional networks in the prefrontal cortex, which normally plays an important role in integrating and broadcasting distributed information [98,104]. Another study found a decrease in functional integration within and between most brain networks, especially in the network between the frontal and parietal cortices [98] and other high-order cognitive networks [99].

Another limitation was the restricted time in which we had to execute SPES under anesthetics. We were able to apply at least two alternating pulses per stimulus pair instead of the ten pulses we applied in SPES-clinical. The effect of the number of trials on N1-peak-latency can be neglected (Supplementary Figure 5). However, the effect of the number of trials on N1-peak-amplitude cannot be ignored and any conclusions on differences between N1-peak-amplitude in the awake state compared to the state under anesthetics should be taken carefully.

Subjects had epilepsy, which may have altered networks [89]. There is no consistent effect of epilepsy on the N1-peak-latency [102], but the epileptogenic region is a densely connected region with high in- and outdegree values [54,89]. Since we

compare the N1-peak-latency, N1-peak-amplitude and network measures within a subject, we assume that a potential effect of epilepsy would be leveled out. Furthermore, on average, only 6% of the electrodes covered epileptogenic regions in our subjects, limiting the effect of epilepsy on our results.

In a study that investigated the depth of anesthesia, a negative correlation was found between the bispectral index and N1-peak-latency and a positive correlation between the bispectral index and N1-peak-amplitude in four patients indicating an increase in N1-peak-latency and a decrease in N1-peak-amplitude when the depth of anesthesia was stronger [95]. In this study, we did not systematically monitor the depth of anesthesia during SPES-propofol. PRIOS03, PRIOS06 and PRIOS07 showed periods of burst suppression, which gradually disappeared, indicating that the level of propofol-anesthesia was not constant.

The amplitude of evoked potentials is decreased during anesthesia [86,101]. This could have complicated the detection of the CCEPs during SPES-propofol. By excluding the burst suppression periods, we compensated for the varying levels of propofol-anesthesia and minimized the risk that CCEPs were missed due to smaller amplitudes of CCEPs. Future studies could give more insight in the working mechanisms of anesthesia on brain networks if we continuously monitor dose-dependent effects of anesthesia on CCEPs and network characteristics. In a future prospective study, brain target-controlled infusion or Bispectral Index Monitoring could be used to estimate different states of consciousness and the depth of propofol anesthesia [105].

In summary, our results show that the number of evoked CCEPs decreased, but this minimally affected the topology of the effective networks derived under propofol-anesthesia. The N1-peak-latency is increased when SPES is applied under propofol-anesthesia, but no clear effect was found on N1-peak-amplitude. More research investigating dose-dependent effects could expand our understanding of how propofol affects effective brain networks.

Supplementary material

DEVELOPMENTAL TRAJECTORY OF TRANSMISSION SPEED IN THE HUMAN BRAIN

Developmental trajectory of transmission speed in the human brain

D. van Blooijs*, M.A. van den Boom*, J.F. van der Aar, G.J.M. Huiskamp, G. Castegnaro, M. Demuru, W.J.E.M. Zweiphenning, P. van Eijsden, K. J. Miller, F.S.S. Leijten, D. Hermes

** These authors contributed equally*
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Abstract

The structure of the human connectome develops from childhood throughout adolescence to middle age, but how these structural changes affect the speed of neuronal signaling is not well described. In 74 subjects, we measured the latency of cortico-cortical evoked responses across association and U-fibers and calculated their corresponding transmission speeds. Decreases in conduction delays until at least 30 years show that the speed of neuronal communication develops well into adulthood.

The development of rapid communication between human brain regions is essential for cognitive function. The speed of neuronal transmission is fundamental to the temporal organization of neuronal activity [106] and is a core component in many computational human brain models [107]. The developing axons in the human brain support rapid neuronal transmission, influencing whether electrical signals arrive at the same or at different times and shaping the timescales of functional connectivity [108]. However, little is known about the maturation process of transmission speed in the human brain, partially because the axonal diameter in the adult human brain is relatively large compared with most other mammalian species [109].

Anatomical studies indicate that the structural human connectome follows a long developmental trajectory: postmortem studies have shown that myelination starts in the late prenatal period and continues into late adolescence [110]. Magnetic resonance imaging (MRI) analyses have demonstrated that white matter properties change across the life-span [111], often reaching a plateau around 30 years of age.

However, electroencephalography (EEG) and magnetoencephalography (MEG) studies that approximate transmission speed by measuring the latency of visual evoked potentials, show highly variable ages at which development plateaus. While studies consistently find decreases in the latency of the visual evoked potential at around 100 ms during infancy and early childhood (<13 years) [112–114], the developmental plateau at which latency decreases change to latency increases differs across studies. Some studies report that evoked potential latency starts increasing after age 13 [115], others report no change in latency during adolescence [116,117], others report that latency decreases up to age 20 followed by an increase [118–120], while others report that latency decreases up to age 40- years [121,122] (Supplementary Table 2). One cortico-cortical evoked potential (CCEP) study reported that conduction delays in subjects older than 15 years were only 1ms faster compared with younger subjects [123]. This poses the question of whether the long structural maturation process translates to changes in neuronal transmission speed.

To characterize the maturation process of transmission speed in the human brain, we measured single pulse stimulation evoked CCEPs during human intracranial electrocorticography (ECoG) recordings in a large group of 74 subjects aged 4-51 years old. CCEPs often show an early surface negative deflection (N1) within 100 ms after stimulating another electrode pair. Figure 1B shows an example of how the N1 response measured in frontal areas upon parietal stimulation peaks around 45 ms in three young subjects (aged 4, 7 and 8-years), while peaking around 1.5-2 times faster, around 25-30 ms, in three older subjects (aged 26, 34 and 35-years).

This rapid negative N1 potential measured with ECoG on the brain surface has been related to direct cortico-cortical white matter connections [44], and is thought to

be generated by synchronized, excitatory synaptic activation of the distal layer apical dendrites of the pyramidal cells [124]. While this feature selection likely ignores many other aspects of the evoked potential that provide a richer characterization of cortico-cortical communication [125], the N1 response provides insight into transmission speed across several bundles in the human white matter connectome [123,126].

To quantify age-related changes in conduction delays across some well described association fiber bundles, we use a white matter atlas to extract CCEPs across the arcuate fasciculus (AF), two sections of superior longitudinal fasciculus (SLF) and the temporo-parietal aslant tract (TPAT) in each subject [127] (Figure 1A). The SLF was segmented into frontal-parietal and frontal-central connections given the different lengths of these segments. We find that N1 latency correlates negatively with age across all four pathways (Figure 1C, Spearman's ρ, $P_{FDR} < 0.05$). We note that the number of CCEPs does not change consistently with age, indicating no age-related changes in the overall level of connectivity (Supplementary Figure 2). The latency decreases show that conduction delays across association fibers in the human brain decrease with development.

We then describe the maturation process across these association fibers by fitting a first- and second-order polynomial model where age predicts N1 latency (Figure 2). These models have been used before in MRI studies of development [111,128]. A robust regression and leave-one-out cross-validation further ensures that single subjects do not drive the results and lets the data indicate which connections are better described by a linear or quadratic model. N1 latency is well predicted by age in the AF, frontal-parietal SLF, frontal to central SLF and TPAT. Moreover, conduction delays mature well into adulthood. Before the age of 10 years, latency decreases by around 0.73 ms per year on average, while between age 20 and 30 years, latency decreases less rapidly by around 0.43 ms per year on average. The quadratic models indicate that a minimum latency of around 25 ms was reached after age 30 years. These small, yearly changes in conduction delays translate in an increase in transmission speed from childhood (6-13 years) to adulthood (19-64 years) or around twofold from roughly 1.5-3 m/s to 3-6 m/s (Figure 2). This indicates that the development of rapid transmission speed across long-range association fibers matures well throughout adolescence.

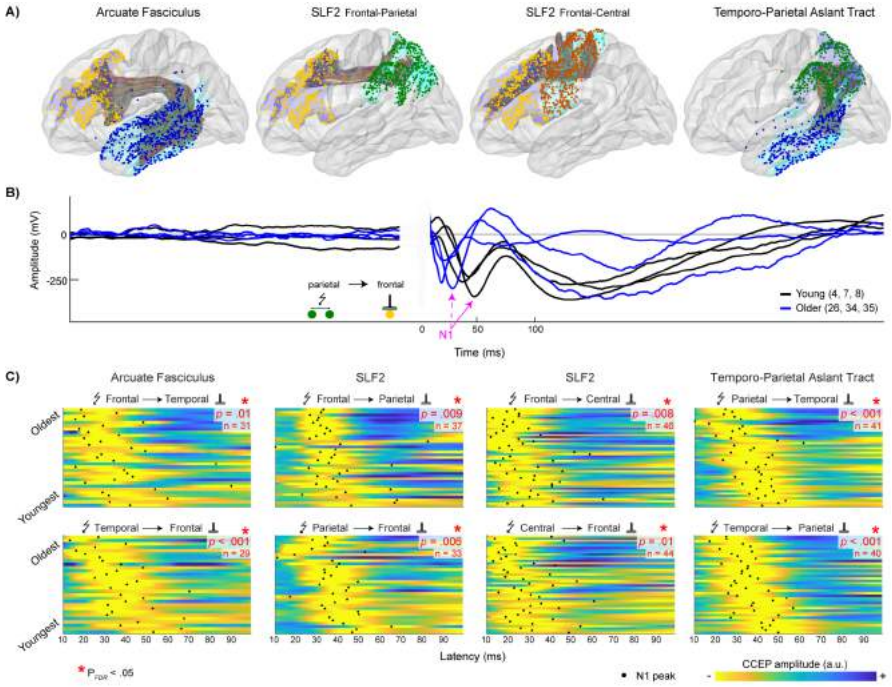


Figure 1. Electrode positions, fiber tracts and evoked potentials. A) MNI brain surface showing white matter tracts and electrode positions at endpoints from all 74 subjects. B) CCEPs from young subjects (black lines, 4, 7 and 8 years old) and older subjects (blue lines, 26, 34 and 35 years old) across the SLF frontal-parietal tract after parietal stimulation. The N1 peak is indicated by a magenta arrow. C) CCEP responses for all subjects and their N1 peak latency (black dots), organized by age for each white matter tract and direction. CCEPs are unit length normalized and yellow indicates the largest negative deflection. A red asterisk indicates a significant negative correlation between age and N1 latency (Spearman's ρ, two-sided, P < 0.05, FDR correction for multiple comparisons). The statistical values from left to right, top to bottom are: ρ = -0.43, P = 0.01, n = 31; ρ = -0.43, P = 0.009, n = 37; ρ = -0.40, P = 0.008, n = 46; ρ = -0.64, P < 0.001, n = 41; ρ = -0.62, P < 0.001, n = 29; ρ = -0.48, P = 0.006, n = 33; ρ = -0.37, P = 0.01, n = 44; ρ = -0.61, P < 0.001, n = 40.

Short-range connections across neighboring gyri such as the pre- and post-central gyrus and within frontal and parietal regions are supported by U-fibers. Latencies decrease significantly with age across these short connections (Figure 3A-B), with corresponding increases in speed (Figure 3C). U-fibers overall reached speeds up to around 2 m/s. The model fits show that latencies decrease until age 35 years or older, indicating that transmission speeds across U-fibers mature well throughout adolescence. Interestingly, the frontal and parietal U-fibers had longer latencies during early childhood (>40 ms) compared with the central U-fibers. This is consistent with the idea that sensorimotor regions mature before frontal and parietal association areas [129].

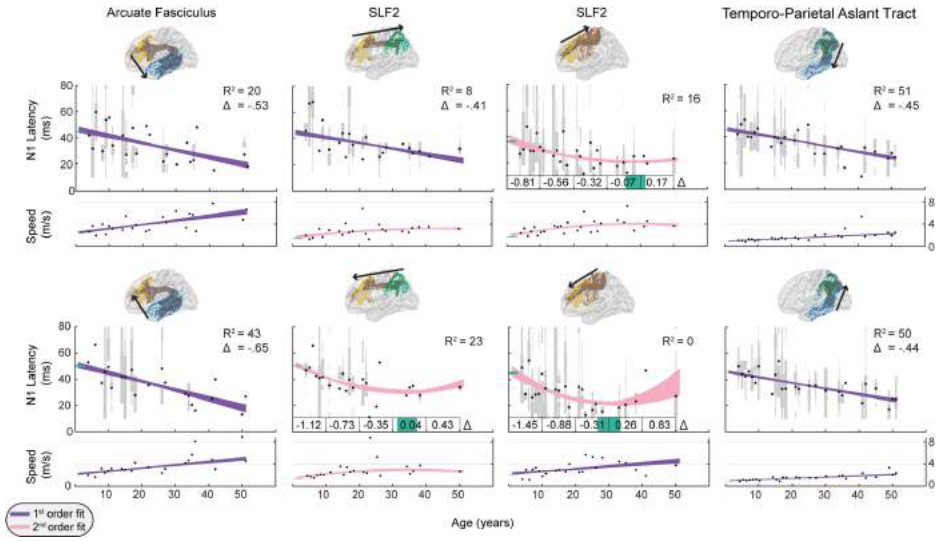


Figure 2. Developmental trajectory of conduction delay and speed across long-range connections. Average transmission latency and speed estimated by the N1 component for the AF, frontal-parietal SLF, frontal-central SLF and TPAT (left to right). Gray bars show distributions within each subject, the bar width scales with the number of measured responses. Black dots show N1 latency or speed averaged across subjects of the same age. First- and second-order polynomial models (fit with robust regression and shown with 95% confidence intervals) explain the changes in N1 latency or speed as a function of age. The coefficient of determination (R^2) indicates the variance in latency explained by age (compared with a mean latency rather than a zero baseline). The R^2 is calculated with leave-one-out cross-validation and used to indicate whether the first-order (purple) or second-order (pink) polynomial model explained more variance in the data. For second-order polynomial model fits, the 95% confidence interval is shown in green for the minimum age on the x-axis and for the N1 latency intercept on the y-axis. For the first-order polynomial fits, insets show the slope change (Δ) in ms per year. For the second-order polynomial fits, the slope change is displayed in ms per year averaged across ten years of age. The sample sizes (n=number of ages) for the top row are: 23, 23, 27 and 26 (from left to right), and 21, 22, 23 and 26 (from left to right) for the bottom row.

While the overall developmental trajectory of the U-fibers was comparable with that of association fibers, there were also important differences. The latencies across the longest association fibers (AF and parietal-frontal SLF) during childhood range from around 45 to 55 ms (Figure 2), while the childhood latencies of central U-fibers range from around 30 to 40 ms (Figure 3B). However, at adulthood, latencies of 20-30 ms are typical for both association and central U-fibers. The maximum speeds reached across the U-fibers (around 2-3 m/s) are therefore smaller compared with the longer range association fibers (around 3-6 m/s). Axon diameters show large variations ranging from 0.16 to 9 μm in the human brain and, given the limitations of the cranial space, only a small number of large axons can have a larger diameter

[106,109]. In myelinated axons, the conduction velocity increases approximately linearly with axon diameter [130]. Smaller U-fiber axons compared with larger association fiber axons may explain the slower speeds in the U-fibers.

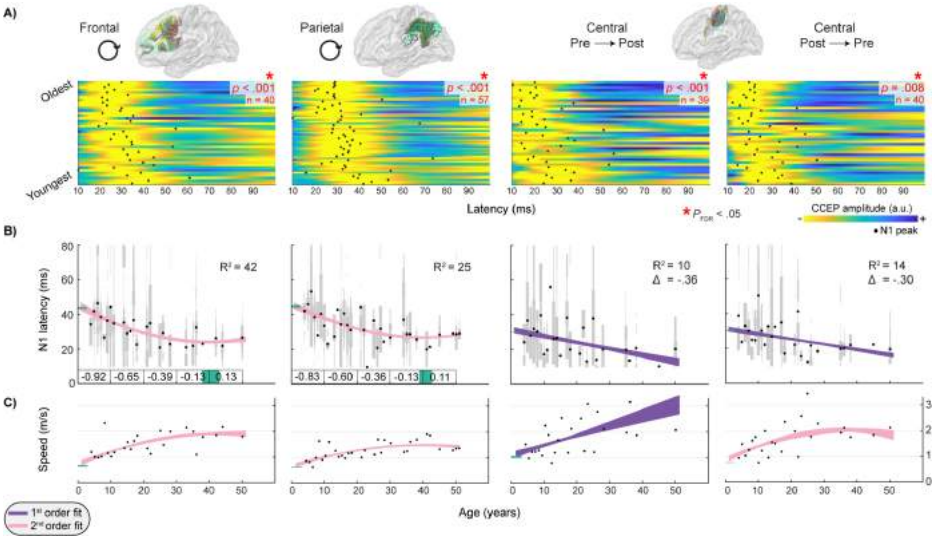


Figure 3. Short-range connections decrease in conduction delay with age. A) The CCEP responses and their N1 peak latencies (black dots) ordered by age for atlas-based U-fiber connections on frontal, parietal, pre- to postcentral and post- to precentral regions. CCEPs are unit length normalized and yellow indicates the largest negative deflection. A red asterisk indicates a significant negative correlation between age and N1 latency (Spearman's ρ, two-sided test, FDR corrected, $P_{FDR} < 0.05$). The statistical values from left to right and the number of subjects n are: ρ = -0.55, P < 0.001, n = 40; ρ = -0.53, P < 0.001, n = 57; ρ = -0.53, P < 0.001, n = 39; ρ = -0.43, P = 0.008, n = 40. B) Average conduction delays estimated by the N1 latency. Gray bars show distributions within each subject, bar width scales with the number of measured responses. Black dots show N1 latency averaged across subjects of the same age. First- and second-order polynomial models (shown with 95% confidence interval) explain the changes in N1 latency as a function of age. The sample sizes (number of ages) are 25, 32, 25 and 25 from left to right. Explained variance (R^2) calculated with leave-one-out cross-validation indicates whether the first-order (purple) or second-order (pink) polynomial model explains more variance. For all model fits, the 95% confidence interval of the N1 latency intercept (latency at the youngest age) is shown in green on the y-axis. For the first-order polynomial fits, insets show the slope change (Δ) in ms per year. For second-order polynomial model fits, the 95% confidence interval of the minimum age is shown in green on the x-axis and the slope change is displayed in ms per year averaged across ten years of age. C) Same as B) for transmission speed based on the average U-fiber length (m/s) and the same sample sizes.

The data reveal variability within and between the subjects. Some variability can probably be attributed to a heterogeneous subject population with different axonal properties and noise levels. Other variability may be explained by the fact that, in many natural processes, increases in the mean are related to increases in variability (such as firing rates typically following a Poisson distribution [131]). We indeed find that slower N1 responses often had increased variance (Supplementary Figure 4) and increased widths (Supplementary Figure 5), while we found no evidence for a relation between subject's age and variance in latency (Supplementary Figure 3). This indicates that faster cortico-cortical connections allow for overall more precise timing, whereas timing is less precise in slower cortico-cortical connections.

Our data indicate that transmission speeds are still maturing during adolescence and early adulthood. Many psychopathologies, like schizophrenia, anxiety disorders, depression, and bipolar disorders, can emerge during these periods [132], emphasizing the potential importance of our findings for these diseases. We note that, while our subjects suffered from epilepsy, there were no consistent effects of the seizure onset region on latency (Supplementary Figures 6 and 7), and epilepsy may merely have added noise to the estimates. The large number of subjects allows us to establish a normative baseline to which different pathologies may be compared.

A long maturation process of transmission speed aligns with findings from non-invasive neuroimaging studies that show that association white matter pathways in the human brain mature well into early adulthood [128,133,134]. MRI studies of the white matter pathways have captured some of these processes and show that white matter development follows a quadratic function with a peak between 30 and 40 years of age [111,135]. This trajectory is comparable with the developmental trajectory of conduction delay that is shown in our data. While this long developmental trajectory is consistent with some evoked potential studies [121,122], other early sensory evoked potentials may show a much faster developmental trajectory until the age of about 20 years [115,118–120]. Some of the variability between evoked potential studies may stem from the development of intermediate synapses between the sensory input and brain measurements. Alternatively, the fast development of some early sensory evoked potentials could also be related to the fact that projection fibers to sensory regions develop faster compared with association fibers [128,133]. Sensory evoked potentials that spread across projection fibers to sensory regions may mature more rapidly compared with the stimulation-evoked potentials across the association fibers measured in the current study.

A simple characterization of the timing of direct cortico-cortical interactions has large implications for the temporal dynamics of brain function. Neuronal synchrony

depends on the precise timing, and development can therefore either benefit or deteriorate synchronized brain activity [106]. Twofold increases in the speed of transmission were observed in long-range as well as short-range connections in the human brain. The large, consistent effects of age on transmission speed in our measurements provide normative estimates for the timescales of cortico-cortical signaling in distributed as well as local human brain networks.

Methods

Subjects

All subjects who underwent epilepsy surgery in the University Medical Center (UMC) Utrecht between 2008 and 2020 were included in a retrospective epilepsy surgery database [96], with approval of the Medical Research Ethical Committee of UMC Utrecht. For subjects included between January 2008 and December 2017, the Medical Research Ethical Committee waived the need for informed consent. Since January 2018, we explicitly ask subjects informed consent to collect their data for research purposes. No statistical methods were used to pre-determine sample sizes and we included all subjects who underwent Single Pulse Electrical Stimulation (SPES) for clinical purposes during the intracranial grid monitoring period between 2012 and 2020 and met inclusion criteria. Subjects were not provided with compensation. In total, 74 subjects were included in this study (median age: 17 years (4-51 years), 38 females), thus spanning age ranges from childhood (6-13 years), adolescence (14-18 years), young adult (19-33 years) and middle age (49-64 years) [136]. Inclusion criteria were the absence of large brain lesions and that electrode positions could be determined based on a computed tomography scan co-registered with a T1 MRI [137]. After electrode localization, electrodes were labeled according to the Freesurfer based Destrieux atlas segmentation [138,139]. The electrodes were well distributed across the age groups (Supplementary Figure 9). For visualization, the individual subject's electrode positions were converted to MNI152 space. During the evaluation for epilepsy, the seizure onset zone and eloquent cortex are delineated and a resection area is suggested to the surgeon. No different experimental conditions were applied to the subjects and randomization was not possible. Data collection and analysis were not performed blind to the conditions of the experiments.

All CCEPs were reviewed and 4 runs with incorrect stimulation onsets were removed. Furthermore, electrodes that overlapped with another grid, were located on small structural abnormalities or had excessive noise were excluded from analyses. On average, across all subjects, 6.3% of electrodes were excluded. We additionally excluded stimulation pairs that introduced baseline offsets on many measured channels. To ensure that the epilepsy did not affect the result in

a systematic manner, the seizure onset zone was annotated in 30 subjects by a clinical neurophysiologist. This allowed comparison of latencies in and outside of the seizure onset region (Supplementary Figures 6 and 7).

Acquisition

Long-term ECoG data were recorded with subdural electrode grids and strips of 4.2 mm^2 contact surface and an interelectrode distance of 1 cm (Ad-Tech and PMT). Additional depth electrodes were implanted in several subjects but were not included in analyses because they were typically placed in lesions visible on an MRI. SPES was performed during ECoG recordings with data sampled at 2048 Hz using a MicroMed LTM64/128 express EEG headbox with integrated programmable stimulator (MicroMed, Mogliano—Veneto, Italy). The stimulation onset was determined accurately by MicroMed hardware, but we note that electrical stimulation creates an artifact from about -9 ms to 9 ms around stimulation onset as channels are coupled to the ground during stimulation. Ten monophasic stimuli with a pulse width of 1 ms were applied at a frequency of 0.2 Hz to two adjacent electrodes. Polarity was alternated after five pulses in 27 of the subjects such that stimulation artifacts are reduced by averaging. A current intensity of 8 mA was used, but in case electrodes were located near central nerves or in the primary sensorimotor cortex, the intensity was lowered to 4 mA to avoid pain or twitches. Changes in amplitude did not systematically influence the results (Supplementary Figure 1).

N1 latency calculation

To estimate conduction delays across different connections, we calculated the latency of the earliest surface negative deflection in the CCEP in 9-100 ms after stimulation. This response is also referred to as the N1 and is thought to be generated by synchronized, excitatory synaptic activation of the distal layer apical dendrites of the pyramidal cells [124,126] and spread through white matter [44,140]. For each electrode, ten epochs with a time window of 2 s pre-stimulus to 3 s post-stimulus, time-locked to the stimulus, are corrected for baseline (median signal in a time window of 900 ms prior to stimulation (-1 s to -0.1 s) and averaged for each stimulus pair [89]. For each averaged epoch, the median is subtracted (-2 s to -0.1 s), and the standard deviation (SD) is calculated in this pre-stimulus window. N1s are detected when the evoked response exceeds 3.4*SD in a time window of 9-100 ms post-stimulation, excluding earlier times due to potential stimulation artifacts.

Stimulation artifacts can potentially spread to nearby electrodes through volume conduction and the following helped ensure that this did not affect our results. First,

volume conduction effects are largest in the first 1-8 ms after electrical stimulation [141], and N1 detection was done after this time, from 9 to 100 ms. Second, we excluded electrodes within 13 mm from the stimulated electrode pair, at which distance the effects of volume conduction are largely negligible [142]. Lastly, in a previous manuscript using a subset of these data, we ensured that volume conduction did not play an important role, by showing that the latencies differ across measured electrodes for a single stimulated pair [143]. We apply a similar method and show in Supplementary Figure 8 that the detected N1 latencies varied across measured electrodes.

While the CCEP waveform has more complex features, the N1 component is the most robust and relevant feature to answer questions about direct electrical conduction [123]. The N1 is measured robustly with ECoG at the brain surface and can be detected as early as 10 ms after stimulation onset. The N1 has been related to direct cortico-cortical connections in many other CCEP studies of, for example, the motor system [43], cingulum bundle [144,145], frontal aslant tract [146] and the superior longitudinal fasciculus [90]. Moreover, previous studies showed that N1 corresponds relatively well with diffusion-MRI derived white matter endpoints [147], the N1 latency relates linearly with the distance traveled along a fiber bundle [73,148], and that the N1 propagation velocity correlates with fractional anisotropy in the white matter [140].

Integrating electrode locations with a white matter atlas

The connectivity between the frontal, temporal, parietal and pre/post-central (primary sensorimotor) areas was investigated based on the arcuate fasciculus (AF), the superior longitudinal fasciculus (SLF) and temporo-parietal aslant tract (TPAT). We focus on these connections, and exclude connections to regions without sufficient electrode coverage for across-subject correlations, such as the occipital lobe. Each of these tracts was defined based on the population-averaged tractography atlases HCP1065 (AF, SLF, TPAT) [127] and HCP842 (U-fibers) [103]. The SLF was split into two sections connecting frontal and parietal and frontal and central brain regions, because merging these sections would lead to inaccurate estimates of the length of the SLF and bias transmission speed estimates described in the next section. We subsequently matched the ECoG electrodes, located on the gray matter surface, to the tractography atlas using the gray matter endpoint probability estimates of the tracts [127]. In this way, we were able to investigate the CCEP based connectivity for different fiber tracts.

Transmission speed estimation

To estimate the transmission speed along the tracts, we calculated the tract length in each subject. Using ANTs registration implemented in lead-dbs [149] between the

subject MRI and MNI space, the tracts from the atlases were registered to the native space of each subject. In each subject's native space, the length of each tract was then calculated by taking the average length over all tract fibers in native space. To estimate transmission speed, the latency of each CCEP along a specific tract was divided by the respective length of the tract to obtain a speed in meters per second.

Statistics

In order to describe the relations between age and conduction delay, and/or age and transmission speed, we fit a first- and second-order polynomial model where age predicts the N1 latency or the transmission speed. These models have been used before in MRI studies to characterize development-related changes in gray and white matter properties [111,150]. Fitting these models with leave-one-out cross-validation lets the data indicate whether the development of different connections is better described by a linear model or a quadratic model with a local minimum. To ensure that certain datapoints with high leverage did not unduly influence the results, we performed a robust regression with bisquare weight function and a tuning constant of 4.685. Data distribution was assumed to be normal but this was not formally tested. The coefficient of determination (R^2) was used to indicate how well the model described the data:

$$R^2 = 1 - \frac{SS_{res}}{SS_{tot}}$$

in which,

$$SS_{res} = \sum_i (y_i - f_i)^2 \text{ and } SS_{tot} = \sum_i (y_i - \bar{y})^2 .$$

We note that the R^2 provides the explained variance relative to a baseline model which predicts the average $\bar{y}$. If the model predicts the data better than baseline, R^2 will be larger than 0, if the model predicts the data worse than baseline, R^2 can be smaller than 0. The R^2 therefore indicates how much of the variance in latency is predicted by age as compared to no change with age. When necessary, statistical tests were corrected for multiple comparisons using a False Discovery Rate (FDR) correction.

Data Availability

The data that support the findings of this study are being made available in BIDS format on OpenNeuro: https://openneuro.org/datasets/ds004080. Atlases of white matter tracts were defined based on the population-averaged tractography atlases HCP1065 (AF, SLF, TPAT) [23] and HCP842 (U-fibers) [50]: https://brain.labsolver.org/hcp_trk_atlas.

Code Availability

The code to analyze the data and generate all figures of this manuscript is available on GitHub: https://github.com/MultimodalNeuroimagingLab/mnl_ccepBids

Supplementary Materials

PART 2: NEUROSTIMULATION AS TREATMENT FOR EPILEPSY PATIENTS

NEOCORTICAL ELECTRICAL STIMULATION FOR EPILEPSY: CLOSED-LOOP VERSUS OPEN-LOOP

Neocortical electrical stimulation for epilepsy: closed-loop versus open-loop

Dorien van Blooijs*, Albena Vassileva*, Frans Leijten, Geertjan Huiskamp

** These authors contributed equally*
Epilepsy Res. 2018 Mar;141:95-101.

Abstract

The aim of this review is to evaluate whether open-loop or closed-loop neocortical electrical stimulation should be the preferred approach to manage seizures in intractable epilepsy.

Twenty cases of open-loop neocortical stimulation with an implanted device have been reported, in 5 case studies. Closed-loop stimulation with an implanted device has been investigated in a larger number of patients in the RNS System clinical trials. With 230 patients enrolled at the start of the Long-term Treatment Trial, 115 remained at the last reported follow-up. Open-loop stimulation reduced seizure frequency in patients on average with over 90% compared to baseline. Closed-loop stimulation reduces seizure frequency with 60%-65%.

Even though open-loop neocortical electrical stimulation has only been reported in 20 patients, and closed-loop in much a larger sample, evidence suggests that both approaches are effective in reducing seizures. It remains an open question which should be clinically preferred. Therefore, a head-to-head adaptive clinical study comparing both approaches is proposed.

Introduction

Intractable epilepsy is a condition in which seizures cannot be controlled by anti-epileptic drugs (AEDs). Perhaps the most effective treatments for those patients are resective surgery and laser ablation [151,152] of the epileptogenic tissue. However, for some patients, surgery might fail to control seizures, due to mislocalisation of the epileptogenic focus [153], insufficient resection, as well as other factors [154]. When surgery is ineffective or not recommended, electrical stimulation has been used as an alternative treatment for medically intractable epilepsy. The most prevalent method is vagus nerve stimulation (VNS). Another is deep brain stimulation (DBS), and targets that have been chosen include the hippocampus, anterior thalamic nuclei, centromedian nucleus, caudate nucleus and the cerebellum. Non-invasive transcranial magnetic stimulation (TMS) generates intracranial electrical currents that may similarly influence cortex excitability [29] and could decrease seizure frequency [155]. Since TMS is not a wearable device, it is outside this review.

An alternative method to manage seizures is by cortical electrical stimulation (CES) directly to the seizure focus. It has been shown that electric pulses can suppress epileptiform activity [156–162] or reduce seizure rate after short-term continuous CES [25,163]. CES can be performed either in an open-loop, or in a closed-loop approach. The open-loop method uses pre-scheduled stimulation, irrespective of ongoing electrophysiological activity in the brain. It is also referred to as "chronic" stimulation, when it is continuous. VNS and DBS are usually delivered in an open-loop manner. Their targets are not neocortical and are therefore beyond the scope of this review. Neocortical open-loop stimulation for epilepsy is a novel approach, which has not yet been extensively clinically tested.

Closed-loop CES means that stimulation starts in response to signals of an impending seizure. It is hence also termed 'responsive stimulation' and aims at preventing or early termination of the clinical symptoms of seizures. To achieve this, electrical brain activity is continuously monitored with subdural implanted electrodes (electrocorticography (ECoG)). Upon detection of abnormal patterns, CES is delivered to terminate seizure onset. Closed-loop neocortical stimulation has been studied in more patients compared to open-loop.

Available devices

The RNS System (by Neuropace) is currently the only fully implantable responsive neurostimulator. The procedure involves a craniotomy and the implantation of the neurostimulator within the curvature of the skull. The whole device is then covered by the scalp. Two electrode leads are connected to the stimulator to monitor and deliver treatment to up to two seizure onset zones.

In all case studies, Medtronic neurostimulators were used for chronic open-loop stimulation. Unlike the RNS, this stimulator is implanted in the chest, rather than within the curvature of the skull. Although typically used for DBS, ECoG leads can also be attached.

Scope and significance of the review

This review compares open-loop and closed-loop CES, delivered to the neocortical seizure focus. So far, there has been no scientific or medical consensus on which approach is superior to the other, or which method should be preferred in any individual case. Therefore, this review seeks to establish whether open-loop or closed-loop CES should be the clinically preferred method for reducing the frequency and severity of epileptic seizures. The following specific review questions are addressed:

- *Which method, open-loop or closed-loop CES, results in a bigger reduction of seizure frequency and severity in the long-term (more than 1 year after the start of the treatment)?*
- *Which method results in dramatic seizure frequency/severity reduction faster (i.e. how long after onset of treatment)?*
- *Which method carries less risk of adverse effects for the patient?*
- *Which method is more practical from the technical perspective (eg. battery life)?*

Methods

Inclusion criteria

Inclusion criteria for article selection were:

1. *CES to a neocortical seizure focus was performed with an implanted device with the goal of reducing seizure frequency/severity.*
2. *Either open-loop or closed-loop CES was delivered.*
3. *Large sample clinical studies when available, otherwise – case studies.*
4. *Human studies only.*
5. *Data published in original articles, research letters and supplementary material.*
6. *Year of publication: 1990 – 2017.*
7. *Language of publication: English.*

Search strategy

The article search was performed in PubMed. Keywords were: cerebral; cortex; electrical; stimulation. Articles were chosen based on the inclusion criteria. Additional articles were chosen from the reference lists of already included publications.

Data collection and analysis

The data for this review were collected from the results sections of the chosen articles and/or supplementary materials. The data of interest included number of participants, study design, type of seizure, seizure focus location, stimulation parameters, type of treatment (open/closed-loop), duration of treatment, seizure frequency before treatment, percent seizure frequency reduction shortly after onset of treatment (immediately up to 1 year), percent seizure frequency reduction in the long-term (1 year and above after onset of treatment), percent of patients with adverse side effects/adverse events, and, if available, improvements in quality of life, including improvements in cognitive and non-cognitive (eg. motor) functioning. The percentages of seizure reduction between methods were compared. Meta-analyses were not performed due to the different study designs of the chosen articles.

Results

Selected articles

The search in PubMed resulted in 940 articles. After reading titles, abstracts, and total articles, only eight articles were selected for review (for details, see Supplementary materials - Table 1). For the closed-loop paradigm, three publications were chosen, which present the results from the Pivotal RNS System clinical trial and the Long-term Treatment Trial (LTT): [22,164] – Pivotal trial; [165] – LTT trial).

For open-loop stimulation five articles, presenting case reports, were selected: [27] – 1 patient; [28] – 2 patients; [6] – 2 patients; [7] – 2 patients, [30] – 13 patients. To our knowledge, those are the only publications to date which report data from open-loop neocortical electrical stimulation for epilepsy.

Closed-loop stimulation

Study design

The RNS System Pivotal trial started with a 3-month baseline period, in which seizure frequency was evaluated. Patients had to have at least three disabling seizures per month (while on AEDs) to be eligible for implantation. Surgery was performed at the end of the baseline period. It was followed by a 4-week post-op stabilization period with ECoG monitoring and no stimulation. At the end of the monitoring phase, the patients were randomized into a treatment group and sham group. A 4-week stimulation optimization period followed, in which stimulation parameters were adjusted. The blinded evaluation phase started at 8 weeks' post-implant and continued for 3 months. During this period, only the patients in the treatment group received stimulation. The neurostimulators in the sham group

were not programmed to deliver treatment, but patients had undergone sham programming. AEDs were kept constant in the blinded phase. At month 5 after implantation (end of blinded period), all patients transitioned into the open label phase. All patients received stimulation from this moment onwards. AEDs could be adjusted in this period. The end of the open label period continued until 2 years after implantation. The LTT trial scope was from year 2 (end of open label period of Pivotal trial) onwards. The same patients from the Pivotal trial transitioned into the LTT. Some had dropped out. Changes in seizure frequency during both the Pivotal and LTT trials were compared against the pre-implant baseline period.

Patient demographics

A total of 256 patients were implanted with the RNS System. 65 patients were implanted in an initial Feasibility study, which is not discussed here. 191 patients were implanted in the Pivotal trial. 187 of them completed the blinded phase, 182 reached one year post-implant and 175 reached two years post-implant. Participants in the LTT included patients who had completed the Pivotal trial, as well as patients who had participated in a previous Feasibility study, with a total of 230 patients. The number of patients that reached year 6 of the LTT was 115. The mean follow-up period was 5.4 implant years.

Around 50% of patients in both trials had seizure foci on neocortex (specific locations not reported), 7%–had combined neocortical and mesial temporal lobe epilepsy (MTLE). The rest had mesial temporal lobe epilepsy (MTLE). Seizure types included simple partial motor seizures, complex partial seizures and secondarily generalized tonic-clonic seizures. Around one third of patients had prior epilepsy surgery, one third had undergone VNS and one third had been hospitalized for ECoG monitoring.

Stimulation parameters

Stimulation was delivered at 200Hz, pulse width at 160 μs, burst duration of 100msec. Current amplitude was below 4mA in 53.8% of subjects, between 4 and 7.9mA in 34.8% and between 8-11.9mA in 8.7% and 12mA in 2.7% of all patients at the end of the open label of the Pivotal trial.

Seizure reduction

In the first month of the blinded period, there was a 34.2% reduction in seizures for the treatment group. Seizure frequency continued to improve in the three-month post-implantation period (mean -37.9%), which was the end of the blinded phase. In the sham stimulation group, there was an initial effect of 25.2% reduction in seizures, but until the end of the 3-month period seizure frequency increased and was 9.4%

less compared to baseline (mean reduction for blinded phase: -17.3%). Reductions in seizures were similar in those with MTLE and neocortical onsets, in those with one and two seizure onset zones, in patients with and without prior intracranial monitoring, and in those treated with and without prior treatment with VNS or epilepsy surgery.

The median seizure reduction for year 1 was 44%; for year 2, 53%. At the end of the open-label period: 58% seizure reduction was reported for the patients with non-MTLE. MTLE patients had a 55% reduction in seizure frequency. Responder rate (patients with 50% or more reduction in seizures) was 29% for the treatment group and 27% in the sham group during the blinded period. In the last three months of the open-label phase 54% of patients had a reduction in seizure frequency of 50% or more. However, 7% had an increase in seizure frequency of 50% or more, 9% were seizure free over the last three months of the Pivotal trial.

Figure 1 presents the long-term efficiency of closed-loop stimulation. At the first three-month period of year 3 (start of LTT) the median percent reduction of seizures was 60% (n=214 after patient drop-out) and the responder rate for that time point 58%. This responder rate included only the patients currently enrolled in the study. However, the adjusted responder rate, which also included patients who had withdrawn from the trial, was also 58%. At this stage, all implanted patients had the neurostimulator turned on and delivering treatment. The rates of seizure reduction varied between 48% and 66%. For the last three months of the LTT (beginning of year 6), the median percent reduction was 66%. 115 patients reached year 6 in the ongoing study, at the date of publication. The adjusted responder rate at year 6 was 55.6%.

Out of all 256 implanted patients before the start of the trials, 36.7% experienced at least one 3-month or longer seizure-free period, 23% at least 6-month seizure free or longer, and 12.9% were seizure free for at least 1 year. No participant was seizure-free for the entire period of the studies and no improvements in seizure severity were reported.

Adverse effects

The most prevalent adverse effect throughout the trials was infection of the implant site (9.4% of patients). 4.7% of the patients experienced some type of intracranial hemorrhage. The number of implantation-related adverse events was not higher compared to that reported following implantation of intracranial electrodes, epilepsy surgery, or with DBS devices for treatment of movement disorders.

Additionally, 7.8% experienced an increase in complex partial seizures. The frequency of tonic-clonic seizures increased in 5.9% and severity of tonic-clonic seizures increased in 4.7% of the patients. Number of seizure-related adverse events was not higher than in medicinal trials for partial onset seizures.

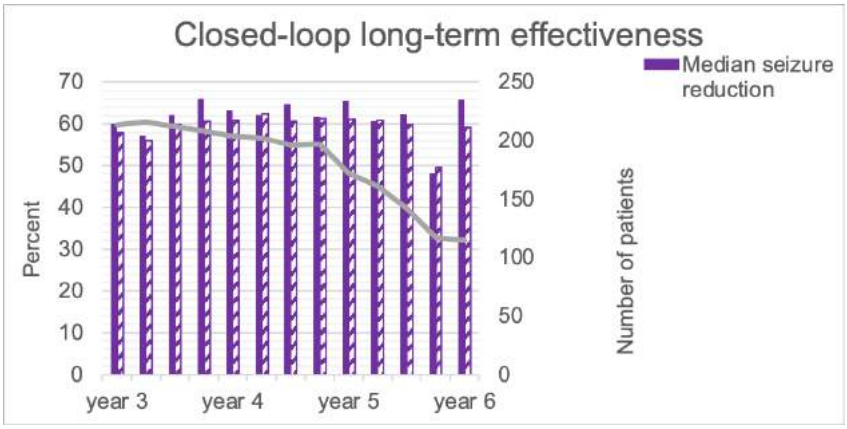


Figure 1: Results from the RNS long-term treatment trial. *Data from [165]. Data is not adjusted for dropped-out patients. Each group of bars represents a three-month period from the beginning of year 3 until the beginning of year 6 (13 3-months periods in total). The filled bars show median seizure frequency reduction compared to pre-implantation baseline. The striped bars represent the responder rate in percent. Responders are patients who have a seizure frequency reduction of at least 50%. The grey line represents the number of patients enrolled at each time point.*

The device had to be removed in 5.5% of patients. Battery was prematurely depleted in 4.3%. Other adverse events reported by Bergey et al.[165], which occurred in more than 2.5% of the patients are death, device lead damage, depression/suicidal (not related to neurostimulation), device lead revision, non-convulsive status epilepticus, pneumonia, convulsive status epilepticus, skin laceration due to seizure, suicide attempt. Number of deaths were not more frequent than expected in patients with refractory epilepsy.

Quality of life

Quality of life improved after year 1 after onset of treatment and remained stable until year 5. Significant improvement was present in the following QOLIE-89 scales: seizure worry, health discouragement, attention, concentration, work/driving/social function, language, role limitation (physical), memory, energy/fatigue, medication effects, overall quality of life.

Open-loop stimulation

Five case studies on open-loop neocortical stimulation were selected, presenting 21 cases in total. One of the cases presented by Child et al.[6] only underwent trial stimulation (authors do not report duration of trial stimulation) and did not get a permanent implant. Therefore, this case was not included in this review. In the scope of this review are 20 cases (14 male, mean age 21, range 6-56) with seizure

foci on primary motor cortex (7), supplementary motor cortex (SMA) (1), with both foci on both eloquent motor and language cortex (1), seizure foci on parietal cortex (3), frontal cortex (2), temporal cortex (2), and one patient with no observed lesion. In three patients reported by Lundstrom et al.[30], only pathology was mentioned: scattered encephalomalacia (1), hemisphere infarct (1), or middle cerebral artery infarct (1). Four patients were diagnosed with epilepsia partialis continua (EPC). Patients had predominantly simple partial motor seizures, secondary tonic-clonic seizures, focal dyscognitive seizures and occasionally secondarily generalized seizures or reflex seizures. One patient had postictal face and corporal paresis (Todd's phenomenon); another had a transient postictal motor disability of the affected arm. Jacksonian march had also been observed in this patient.

Stimulation parameters

Seventeen patients had continuous chronic stimulation. Two patients had cyclic stimulation (1 min on - 4 min off; 3 min on - 10 min off) and one patient first received continuous, and subsequently cyclic (1 min on - 4 min off) to preserve battery life. Pulse rate was between 2 and 130 Hz and pulse width between 90μs and 120ms. Up to 7V and 3mA were used. The minimum current intensity used was below 450 μA [28].

Seizure reduction

Chronic stimulation resulted in a reduction of seizure frequency by more than 90% in 8 out of 16 cases in the first year (Figure 2). One case (female, age 17) with smaller reduction in month 1, became seizure free in month 2, when stimulation intensity was increased from 250μA to 350μA. Another case (male, age 44) was stimulated with 50 Hz and experienced a gradual decrease in seizure frequency, with a mean reduction of around 80% in month 2, around 90% in month 6, and 4 years after implantation, seizures were more than 97% less frequent. The short-term reduction of seizures was not mentioned for one patient [6]. For 3 patients (patient 8, 14, 17 in Figure 2), no seizure reduction was mentioned because these patients had reflex seizures or EPC [30].

All patients experienced dramatic (72-100%) reduction in seizure frequency in the long-term (above 1 year of treatment) (Figure 2). Additionally, postictal events like Todd's phenomenon (2 patients) and motor dysfunction (1 patient) were eliminated. There was also a reduction of over 90% of IEDs in two patients. In another, they gradually decreased until month 12, when they had completely disappeared.

Child et al.[6] and Valentin et al.[7] report that when the stimulator was deactivated (due to battery depletion or inadvertently), seizure frequency increased close to the baseline level, and decreased once treatment was resumed.

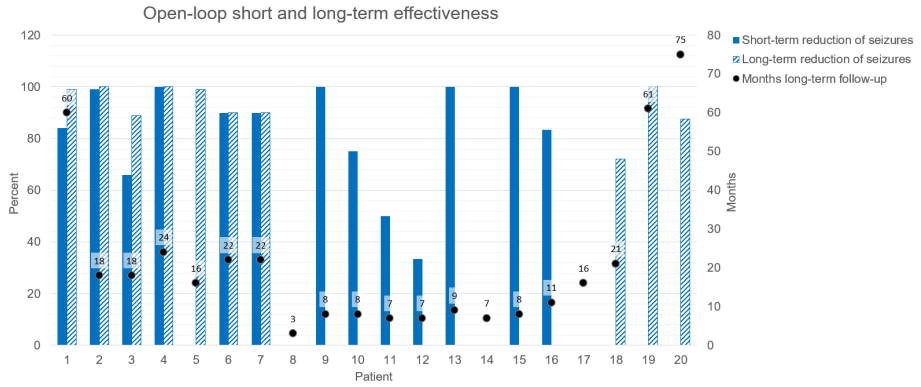


Figure 2: Open-loop short versus long-term effectiveness. *Data from [6,7,27,28,30]. The filled bars represent short-term percent reduction of seizure frequency (within one year post-implantation). Short-term data for patient 5 ([6]), and seizure reduction due to the presence of EPC or reflex seizures for patient 8, 14 and 17 ([30]) was not reported. Striped bars represent long-term percent reduction at last follow-up post-implantation (indicated by the dark boxes and the right vertical axis).*

Adverse effects

There were no adverse effects in any of the cases, neither related to the implantation of the leads or neurostimulator, nor the stimulation itself. The only adverse events occurred when battery was depleted and seizures/EPC reappeared. However, they were resolved once stimulation was resumed.

Quality of life

Velasco et al. [28] measured quality of life before and after treatment using the QOLIE scale for adolescents. For one of the cases (male, age 17), a total of 17.56 improvement was present in the scales impact, memory, stigma, support and health. For the other case (female, age 17), there were improvements in impact, memory, functioning, stigma, support, school and attitudes, with a total of 33 points. It should be noted that the second case had mental retardation. Both patients had aggressive attitudes before the treatment, which were resolved in the first patient.

Lundstrom et al. [30] determined life satisfaction based on patient self-report. Ten of the 13 patients reported increased life satisfaction following chronic stimulation (4.5 (SD:2.2) to 7.2 (SD: 1.6)).

The other case studies did not report formally measured quality of life changes, but observed significant improvements in motor function. One of the patients reported by Valentin et al. [7] had significantly better hand dexterity and fine motor control, and could perform tasks like drawing and writing, which were not possible before, due to

the EPC. The main improvement in the case reported by Elisevich et al. [27] was that the patient no longer had the postictal motor disability of the hand, which prevented him from operating his arm for 30 minutes after seizure-related tonic posturing.

Discussion

Eight articles were selected for review. Three articles reported the RNS System clinical trials, which evaluated closed-loop stimulation for epilepsy. Around 50% of those patients had neocortical epilepsy with varying seizure onset zones. Five case reports on open-loop neocortical stimulation were selected for review, describing the treatment outcome in 20 patients, 8 of which with seizure foci in motor cortex, and 4 with motor seizures but unspecified seizure foci.

Quality of evidence

There is a strong publication bias, as the closed-loop articles reported well-controlled large-sample clinical trials, while the open-loop articles were only case reports. The quality of evidence for the clinical trials was moderate, as the study design did not include control for seizure focus location, which can prove to be important for treatment effectiveness. Due to the descriptive nature of the case reports, their quality of evidence is low. At this point in time, this is unavoidable. Open-loop stimulation has only been extensively used with non-neocortical targets, such as the vagus nerve, the hippocampus, the centromedian nucleus, the caudate nucleus and the anterior thalamic nucleus. To our knowledge, the articles selected in this review [6,7,27,28,30], are the only published data to date on open-loop electrical stimulation delivered to neocortical seizure focus. Those five articles present 20 cases with long-term (aiming at permanent) implantation of a chronic neurostimulator.

Effectiveness of closed-loop versus open-loop

No conclusions can be made based on the currently available data. Until more empirical data and knowledge is accumulated, all discussions are speculative.

Both approaches appear to be effective in reducing seizure frequency in patients with medically intractable epilepsy. However, open-loop neocortical stimulation seems to provide a more drastic change in seizure frequency reduction (on average over 90%). In the short-term, open-loop seems to offer a faster result. However, the RNS Pivotal study showed that there is an initial implantation effect, which drove the reduction of seizures in the first few months. Both the treatment and the sham group experienced less seizures in the short-term. However, the reduction continued to lower for the treatment group, while in the sham – it started rising

again after 3 months. It is very likely that the same effect was also contributing to the results presented in the open-loop case studies. Even so, the seizure frequency reduction in those patients was quite drastic, with some patients experiencing more than 90% less seizures immediately after onset of treatment. One patient who had a delayed response was initially treated with a lower stimulus intensity. When it was increased, seizure frequency dropped. This immediate reduction in seizures after onset of stimulation, with the electrode leads having been implanted for a long period, reduces the probability of a placebo effect.

For the purposes of this review, we considered long-term effectiveness of seizure reduction at the last follow-up that was reported. The open-loop case studies present results from follow-ups between 3 months and 6 years. The RNS clinical trials' last reported follow-up was 5 years and three months (i.e. first three months of year 6). The trial is still ongoing.

The results of the RNS clinical trials show that responsive stimulation increases in effectiveness gradually. At the last follow-up, which was the beginning of year 6, the median reduction in seizure frequency was 65%. During the LTT, this percentage revolved around 60%, but some patients were seizure-free for a period of at least 1 year as well. In comparison, the 20 patients who had undergone open-loop stimulation suffered from at least 90% less seizures. This does not necessarily mean that open-loop is more effective than closed-loop. Most patients (9 out of 10) with a high seizure reduction during long-term treatment had simple partial motor seizures. It is likely that motor cortex responds differently to stimulation. The RNS trials were not powered to compare effectiveness between patients with different seizure foci, but at the end of the open-label phase of the Pivotal trial, the effectiveness of the treatment was similar between MTLE and non-MTLE patients. No data was presented on the effectiveness of treatment between patients with different neocortical seizure foci.

Another possible explanation of the seemingly more effective open-loop approach is that chronic stimulation suppresses tissue epileptogenicity and acts as a form of "medication", by providing continuous neuromodulation. Furthermore, the effects might be sustained. In both cases presented by Valentin et al.[7], reducing and terminating the stimulation did not result in immediate resurgence of EPC. It took several hours or even days for the positive effect of the treatment to vanish. Valentin et al.[25] reported that short-term stimulation (4-6 hours for four days) during intracranial monitoring resulted in seizure freedom for at least 20 months. Closed-loop stimulation does not provide the same continuous neuromodulation.

However, the mechanisms through which electrical stimulation interferes with epileptic seizures and interictal epileptiform activity are still unknown. There is also

variability in the optimal stimulation parameters between patients. Some respond well to high-frequency stimulation, while low-frequency provokes seizures, in others it might be the reverse [6]. This might be related to a plethora of factors, including exact seizure focus, its size, its connectivity patterns etc. Elucidating the mechanisms through which electrical stimulation modulates epileptiform activity in the brain would be greatly beneficial in determining the optimal parameters and approach for individual cases.

Practical considerations

From the viewpoint of practicality of each approach, several things should be considered. Firstly, the adverse effects must be minimal. The RNS clinical trials had a high percentage of implant site inflammation. This is understandable and expected, as the implantation procedure involves a long scalp incision and relatively large craniotomy to make place for the neurostimulator. The RNS battery is not rechargeable through the skin. This means that once it is depleted, the scalp should be opened again to replace the device. This puts the patient at risk every time a replacement is necessary. Another consideration for the RNS is that, as it is placed within the curvature of the skull, it is possible to cause damage to the underlying dura or the overlying scalp tissue. Even though such cases are not common, it is a risk to consider.

The Medtronic stimulator is not rechargeable either, but may be less invasive to replace, as the battery is implanted in the chest. However, this leads to another problem - the system includes wiring that goes around the neck towards the chest. This cable length is more easily susceptible to interference and the battery location can be inconvenient and less aesthetic.

Battery life is perhaps the most crucial technicality to consider, as it relates not only to the risks associated with reopening of the incisions, but also to interruption of treatment. On one hand, closed-loop stimulation can be more efficient in terms of preserving battery life. On the other hand, larger stimulation intensity is used in this modality (starting from 0.5 mA and above until tolerance). In contrast, Velasco et al.[28] used up to 450μA, i.e. just below the starting point of intensity which was used in the RNS trials (see Supplementary materials, Table 2). Since lower intensity means longer battery life, open-loop has the advantage if it decreases seizure frequency even at low amperage.

Another benefit of open-loop is that it does not require a detection algorithm. Within patients, epileptiform activity can manifest in different ways. It is hard to investigate the performance of such detection algorithms when continuous data recordings for months are not available. Long-term continuous ECoG recordings may reveal individual morphology during the pre-ictal and ictal period, and therefore help individual optimization of a detection algorithm [166].

Moreover, it has been shown that less dense electrode grids are unable to detect microseizures, which can progress to large-scale seizures [167]. In this train of thought, the effectiveness of open-loop stimulation does not depend on the detection of epileptiform activity.

One of the concerns regarding continuous stimulation is that it can potentially be damaging to the tissue. Charge density per phase (CDP) has been shown to be the critical variable to consider to avoid damage [168]. The articles reviewed here did not always specify whether CDP was within the safe margins. However, stimulation parameters were similar and therefore CDP must have been below the safe limit. In the open-loop paradigm the neuronal tissue receives much more stimulation in total, compared to closed-loop. Although side effects of the stimulation itself are not common, because the stimulation parameters are carefully optimized for each patient, it is preferable to keep the total exposure to electric stimuli to a minimum.

Perspective on CES for treatment of epilepsy

Around 30% of epilepsy patients cannot manage their seizures with AEDs. Many will not be candidates for resective surgery or laser ablation. Some have tried stimulation methods like VNS, but with limited effectiveness. Today, permanent implantation of electrodes and a neurostimulator is only an adjunctive therapy for epilepsy, alongside AEDs. The RNS clinical trials demonstrated that closed-loop stimulation can be beneficial in many patients and reduces seizure frequency. The five case reports on open-loop stimulation, which were discussed in this review, additionally demonstrate that responsive stimulation is not the only effective approach. No conclusions can be made yet on which one is better and both approaches seem promising.

Closed-loop stimulation can terminate detected seizure activity. Open-loop stimulation provides continuous neuromodulation, which seems to reduce the epileptogenicity of the cortex. To our knowledge, a combination of both approaches has never been tried before. A "hybrid" approach might both reduce seizures and IEDs, and manage seizures that do develop. The ideal result would be for medically intractable patients to discontinue AED treatment. AEDs can have side-effects which worsen the quality of life of the patient. Although stimulation methods are invasive and are usually less preferred than medication-only treatment, they are sometimes the only option for many patients. The "hybrid" approach might be a suitable replacement of AEDs, i.e. it is more effective and with less side effects. If the risks related to implantation are minimized, a combination of open-loop and closed-loop stimulation could be a preferred method for treatment of medically intractable epilepsy.

The challenges that need to be addressed involve primarily the understanding of the mechanisms through which stimulation is beneficial for managing seizures (which would also help optimization of stimulation parameters), minimizing the risks associated with the invasiveness of the procedure, developing better and more efficient algorithms for seizure prediction. Since there is a great variability between patients in their responses to any modality of CES, it is possible that neither approach is the universally better one in all patients.

Further investigation of closed-loop versus open-loop

Further research should focus on optimizing stimulus parameters and responsive stimulation. Responsive stimulation was originally supposed to detect seizure susceptibility and stimulate upon the likelihood of seizure occurrence [169]. Current closed-loop algorithms do not estimate seizure likelihood and respond to this. Cook et al.[170] successfully conducted the first clinical trial of an invasive device dedicated to seizure prediction in 15 patients. Good et al.[171] applied in epileptic rats automated 'just-in-time' stimulation, which is similar to responsive stimulation, except that stimuli were not applied at seizure onset, but when a pathological pre-ictal synchronization was observed (which could be in the order of ten minutes before seizure onset).

Another method to identify seizure susceptibility is by applying TMS to probe cortical excitability. Cortical hyperexcitability is known as a marker for a pre-seizure state [172]. A simulation study by Ehrens et al.[173] detected the transition from stable network mode to unstable mode using the firing rate of the most fragile node in the network. When this network was unstable, they applied a stimulus to stabilize it again. They were able to suppress seizures within 2 s after onset.

Computational models of epileptic network characteristics may provide alternative approaches to determine optimal stimulation parameters and the best location for stimulation. Taylor et al.[174] constructed a state space in which optimal stimulation is based on the amplitude and phase of a spike-wave cycle in spike-wave seizures. Their model proposes an adaptive approach to find optimal stimulation parameters individualized, based on real-time spike-wave detection. Anderson et al.[175] used a neural network simulation to study stimulation parameters and reported that the effect of stimulation is more effective when it is timed close to the negative ECoG peak of seizure activity. Same results were reported for stopping after-discharges which occurred during electrical stimulation mapping [176].

Other improvements may be obtained in optimizing stimulus parameters in individuals. The current neuromodulation approaches apply periodic or responsive stimulations with individualized pre-determined stimulation parameters. Chakravarthy

et al.[177] simulated different electrical stimulation-based control paradigms in which open-loop or closed-loop stimulation with an individualized pre-determined or adaptive stimulation was delivered. The adaptive stimulation outperformed all other paradigms for seizure control in this neural mass network [178]. Instead of determining the stimulus parameters prior to stimulation, adaptive stimulus parameters were determined by analysis of the network global state at the moment of stimulation [179].

To be able to recommend to patients the optimal treatment modality, there must be a thorough understanding of each method. Responsive neurostimulation for epilepsy has been investigated in well-controlled clinical trials, while only five publications report on open-loop stimulation of neocortical seizure foci. This limits the study of the differences and similarities between closed-loop and open-loop in terms of effectiveness and adverse effects. Additional data needs to be collected. The following research questions can be addressed in future studies:

1. *Does open-loop stimulation effectiveness differ from closed-loop?*
2. *Does the location of the seizure focus influence the effectiveness of the stimulation approach?*
3. *Does stimulation effectiveness depend on whether the seizure focus is on or near eloquent cortex?*
4. *What stimulation parameters are the most effective and safe?*
5. *Can neurostimulation potentially be used as an alternative to resective surgery or laser ablation?*

Several factors and variables must be accounted for. First, it is necessary to investigate whether different neocortical seizure foci respond differentially to stimulation. This requires controlling for seizure focus location by including large samples of patients for as many different areas as possible. Another factor that might influence the effectiveness of stimulation is whether the seizure onset zone resides at or near eloquent cortex. Since eloquent cortex connectivity patterns have been proposed to be distinctive [180], they might have a crucial effect on seizure propagation and, therefore, seizure termination.

A head-to-head adaptive randomized design can be employed to compare open-loop and closed-loop stimulation. However, it has some caveats. The first problem is technological - a device that is able to perform both kinds of treatment is required. Patients need to be randomly and blindly assigned to one of the two treatments at the time of enrolment in the study. This is necessary because the closed-loop approach involves a seizure detection algorithm, which needs to be optimized for each patient. If possible, the open-loop and closed-loop groups should be matched

for seizure focus location. AEDs should be kept constant. Additionally, quality of life of patients should be evaluated using a standardized scale.

Conclusion

Electrical stimulation for epilepsy is a promising approach. Although the RNS System already has received market approval in the USA, the mechanisms of action of stimulation with respect to seizure reduction are largely unknown. Despite that, both the open-loop and closed-loop approaches have been shown to effectively and sustainably reduce seizure frequency in patients with medically intractable epilepsy. The two approaches have been investigated in different scales. Only twenty individual cases in which open-loop stimulation was used on neocortical seizure focus have been described. Yet, in most of them the reduction in seizure frequency is dramatic. However, closed-loop stimulation has also been largely effective in some cases. Both approaches are able to eliminate seizures for long period of time. Further research should focus on determining which approach, or combination of both, is the best option for patients with intractable epilepsy. More data needs to be collected in controlled double-blind studies. The potential of electrical stimulation in seizure management is considerable. If proper and optimal parameters and methods are developed, CES might even replace resective surgery or laser ablation in treating intractable epilepsy.

Supplementary Materials

LOCAL CORTICAL NETWORK STIMULATION AS A CONCEPT FOR FOCAL EPILEPSY TREATMENT

Local cortical network stimulation as a concept for focal epilepsy treatment

D. van Blooijs, M.D. van der Stoel, G.J.M. Huiskamp, M. Demuru, N.F. Ramsey, F.S.S. Leijten

Submitted.

Abstract

Background: Electrical stimulation therapy for epilepsy patients is applied either to the epileptogenic region or to a larger network (e.g. with deep brain stimulation).

Objective/hypothesis: Responses to single pulse electrical stimuli (SPES) reveal potential stimulation sites that target the epileptogenic region for cortical network stimulation therapy.

Methods: We applied SPES to ten epilepsy patients who underwent intracranial electrocorticography recordings for pre-surgical evaluation. We detected cortico-cortical evoked potentials (CCEPs) in response electrodes after stimulating other pairs of electrodes, revealing effective connections. We calculated event-related spectral perturbation (ERSP) plots in all response electrodes after stimulating other electrode pairs. We detected interictal epileptic discharges (IEDs) before and after each single pulse and calculated the logarithmic IED ratio.

We analyzed whether power suppression in the ERSP occurred in a response electrode when connected with the stimulus pair. We analyzed whether a larger change in IED ratio was accompanied by power suppression in the response electrode or when this electrode was connected with the stimulus pair.

Results: We found that SPES has a neuromodulatory effect measured as: 1) the relationship of a CCEP and power suppression, 2) a larger change in IED rate when a CCEP was present, 3) a decrease in IED rate when power suppression was observed.

Conclusion(s): Results suggest that stimulation in an area connected to the epileptogenic region can modulate IEDs in this region. SPES might provide a template for localizing a stimulation site outside the epileptogenic region for electrical stimulation treatment of epilepsy.

Introduction

Electrical brain stimulation is a relatively new therapy for patients with epilepsy. Stimulation targets, evaluated for epilepsy, fall into two broad categories representing different therapeutic strategies: 1) focal stimulation, intended to directly affect the seizure onset zone [1]; and 2) global stimulation (e.g. vagal nerve stimulation or deep brain stimulation), where nodes within a larger thalamo-cortical-basal ganglia network are targeted, with the goal of influencing seizure initiation and/or propagation within these pathways [2]. Focal stimulation is thought to be more effective in suppressing seizure activity than global stimulation [3].

Several studies applied focal stimulation with effects ranging from a responder rate of 54% (after two years [4]) to 73% (after nine years of therapy [5]) to an overall seizure frequency reduction of 67% [6] to more than 80% [7–10]. These studies applied electrical stimuli in the epileptogenic region, but the optimal stimulation location for neurostimulation therapy is currently undefined [11]. Perhaps, a local cortical network approach would be beneficial.

The therapeutic effect of neurostimulation may be mediated by specific structural [11] or functional networks [12,13]. When these networks in patients with Parkinson's disease were compared before and after deep brain stimulation, the networks showed topological reorganization towards the networks measured in healthy controls [14]. When neurostimulation in epilepsy patients is applied for a longer period of time, functional networks undergo reorganization in patients that respond well to electrical stimulation [15]. Furthermore, the fact that seizure frequency decreases over time when neurostimulation therapy is effective [5,6] also supports the idea that networks undergo plasticity-related changes resulting in a network that is less prone to evolving seizures [15]. If the potential capability of plasticity-related changes could be measured in the individual patient prior to neurostimulation treatment, this would help in decision making towards a personalized therapy.

Analyses of electrocorticography (ECoG) recordings have shown that the degree of synchronizability of the network could predict the effectiveness of neurostimulation treatment [16]. Another study shows that stimulation in the epileptogenic region was more effective in seizure rate reduction if the node had more connections with other nodes [17]. This suggests that it is important to also look at the underlying network to determine the optimal stimulation site.

An effective network can be derived from single pulse electrical stimulation (SPES) [18] in which single pulses are applied to intracranial electrode pairs. Cortico-cortical evoked potentials (CCEPs) to these stimuli in other electrodes indicate a connection between the stimulus pair and the responding electrode [18]. The

epileptogenic tissue was found to exhibit a higher density of such connections than surrounding tissue [19]. We hypothesize that electrical stimulation in a stimulus pair connected to the epileptogenic cortical network might facilitate plasticity-related changes as described in long-term electrical stimulation studies.

In this study, we investigate whether the existence of an effective connection (by means of an evoked CCEP) between the stimulus pair and a responding electrode facilitates stimulation-induced changes in rate of interictal epileptic discharges (IEDs), and whether it can affect neural activity in terms of spectral power changes. Effects on IEDs and neural activity in general could be of interest as a surrogate marker [20] for electrical stimulation therapy in that it could offer new stimulation target options.

Materials and methods

Patient characteristics

We selected epilepsy patients who underwent electrocorticography (ECoG) recordings for 5-7 days for evaluation of epilepsy surgery between 2014 and 2017. We decoded and visually annotated the data for bad channels, artefacts, seizures and stimulus pairs, and imported this data into the Brain Imaging Data Structure (BIDS) [21,22]. The study was performed with approval from the ethical committee under Dutch law, in accordance with the Declaration of Helsinki (2013).

Acquisition and pre-processing epochs

A Single Pulse Electrical Stimulation (SPES) protocol had been performed in these patients as part of clinical routine to delineate epileptogenic tissue [23]. Ten monophasic pulses (8 mA, 1 ms, 0.2 Hz) were applied to pairs of adjacent electrodes (Figure 1). In the primary sensorimotor cortex, pulse intensity was decreased to 4 mA to avoid tingling or twitches. Electrodes located on top of other electrodes or electrodes with noisy signals were not stimulated and excluded from analysis.

For each electrode, ten epochs in time domain were averaged for each stimulation pair, with a time window of 2 s before to 2 s after the electrical stimulus time-locked to the stimulus (Figure 1B). We detected cortico-cortical evoked potentials (CCEPs, Figure 1C) when the first negative deflection within 100 ms after stimulation exceeded a threshold of 2.6 times the standard deviation that was calculated in an epoch interval of -2s to -0.1s covering pre-stimulus baseline [19,24]. The detected CCEPs were visually checked (DvB).

For each electrode, a wavelet-based time-frequency transformation was applied to ten epochs with a time window of 1 s before to 1 s after the stimulus time-locked to the stimulus for each stimulation pair [25]. This Event-Related Spectral Perturbation

(ERSP [26]) plot used a Morlet wavelet with two oscillation parameters [3 0.8]. The frequency range was set to 10-250 Hz with a frequency resolution of 1 Hz. We applied bootstrapping to observe significant spectral changes post-stimulation compared to pre-stimulation (Figure 1D). We used a trained support vector machine, based on the surface, the duration and the frequency range of an area with power suppression, to detect these significant events of power suppression post-stimulation. The ERSPs with detected power suppression were visually checked (DvB).

Preprocessing interictal epileptic discharges (IEDs)

For each patient, electrodes showing interictal epileptic discharges (IEDs) were determined by a clinical neurophysiologist (FL). We applied an IED detection algorithm based on the algorithm by Gaspard et al. 2014 [27] to the time domain recordings in which the SPES protocol was executed. In each electrode with IEDs, we counted the number of IEDs 1-0.1 s before and 0.1-1 s after stimulation for each individual stimulus. We excluded a symmetric time window of in total 200 ms around the stimulus onset to exclude CCEPs which occur within 100 ms after stimulation and to avoid interference of the stimulus artefact in counting the number of IEDs (Figure 1B). We calculated the ratio (Figure 1E) by dividing the number of IEDs post-stimulation by the number of IEDs pre-stimulation across the ten pulses to each stimulus pair. We converted the ratio to a logarithmic scale: a value of 0 means that no change was observed in number of IEDs post-stimulation compared to pre-stimulation; a value of <0 means a decrease in IEDs after stimulation; and a value of >0 means an increase in IEDs after stimulation.

Analysis

First, we investigated whether CCEPs in a response electrode were accompanied by power suppression in the ERSP after stimulating a certain electrode pair by calculating the odds ratio for all individual patients and all patients combined. Odds ratios were analyzed with chi^2 test and FDR corrected ($p<0.05$). For this analysis, we included all subdural electrodes.

For the following analyses, we only included the electrodes in which IEDs were observed. We investigated whether the occurrence of a CCEP was accompanied by a change in IEDs post-stimulation. We separated IED electrodes with and without a CCEP and analyzed whether the distribution of IED ratios was statistically different with a Kolmogorov-Smirnov test. If both distributions differed, we analyzed this difference in more detail. We compared the absolute values of logarithmic IED ratio, defined as either increase or decrease in IED ratio, to explore general changes in neuromodulation

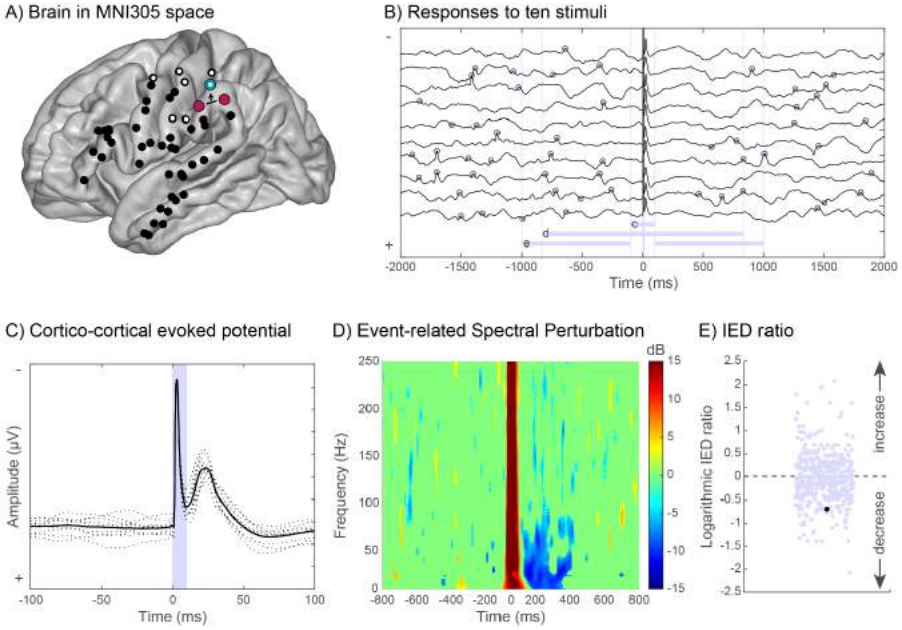


Figure 1: overview of one patient. *A) the grid electrodes in MNI305 space. The electrodes with a white dot are the electrodes in which IEDs were observed. The purple electrodes are stimulated and the responses in the blue electrode are shown in B). In B), ten responses of 2 s pre- and 2 s post-stimulation are displayed. The gray dots indicate the detected IEDs. We observed that the number of IEDs seemed to be reduced during 500 ms after stimulation. The time windows in which respectively CCEPs, power suppression in ERSP, and IED ratio are determined are visualized with gray bars at the bottom of this figure. C) Ten single cortico-cortical evoked potentials (CCEPs) (dotted lines) of B) and the average response (black line) are visualized in a time window of 100 ms pre- and 100 ms post-stimulation. The peak at ~30ms after stimulation is called the N1 peak and is the first negative deflection that is characteristic for the CCEP. The gray vertical bar between 0 and 10 ms displays the time window in which the stimulus artefact is visible. D) An Event-Related Spectral Perturbation (ERSP) plot is constructed based on the ten epochs in B). The red bar at 0 ms indicates the stimulation artefact. The blue area after the stimulation artefact indicates a significant suppression in power compared to the time window pre-stimulation. This suppression is present in the frequency band from 1 to ~100 Hz during 400 ms after stimulation. E) The logarithmic IED ratios of this specific subject are displayed in gray. The black dot indicates the logarithmic IED ratio derived from the ten epochs in B). During 1 s pre-stimulation, 14 IEDs were detected, during 1 s post-stimulation 7 IEDs were detected, resulting in a logarithmic IED ratio of -0.69.*

that might be induced when an IED electrode is connected with the stimulus pair. We also compared the positive values of logarithmic IED ratio, which means only an increase in IEDs post-stimulation, and the negative values of logarithmic IED ratio, which means only a decrease in IEDs post-stimulation to investigate whether a specific effect of neuromodulation was induced when an IED electrode was connected to the stimulus pair. Comparisons in logarithmic IED ratios were analyzed with the Mann Whitney U test and FDR corrected ($p<0.05$). We also separated IED electrodes with and without the occurrence of power suppression after stimulation of stimulus pairs and repeated the statistical analyses on IED ratios as described earlier.

Finally, we investigated the number of IEDs in time. We wanted to analyze how long a change in IED count post-stimulation compared to pre-stimulation would last. Therefore, we counted the number of IEDs in an epoch of 2 s pre- and 2 s post-stimulation instead of 1 s pre- and post-stimulation, as was used for the logarithmic IED ratio. We categorized response electrodes into four categories: 1) with evoked CCEP and power suppression, 2) with evoked CCEP and without power suppression, 3) without CCEP and with power suppression, 4) without CCEP and without power suppression. We calculated how many IEDs were observed on average during the 2 s pre-stimulation. We divided the 2 s post-stimulation time window in periods of 200 ms and calculated how many IEDs were observed on averaged in each period for each category. We compared the number of IEDs in each consecutive time window of 200 ms post-stimulation with the mean number of IEDs pre-stimulation. Comparison in number of IEDs in consecutive time windows were analyzed with a paired t-test and FDR corrected ($p<0.05$).

Code and data availability

All code is available at https://github.com/dvanblooijs/CCEP_suppressionPower_Spikes. Data is available at openneuro.org.

Results

Patient characteristics

We included ten patients (6 males, median age 15 years (range: 9-41 years)), see Table 1. ECoG was performed with subdural platinum circular electrodes with 4.2 mm^2 contact surface, and an center-to-center electrode distance of 1 cm (AdTech). Electrode grids were placed on the brain areas suspected of seizure onset. A median number of 64 (range: 54-96) electrodes were implanted per patient. In four patients, depth electrodes (1-2 leads with 6 electrodes each) were placed in the presumed lesion that was visible on MRI. Data were recorded with a sampling frequency of

2048 Hz. In seven patients, a median number of 8 electrodes (range: 6-19) were covering areas generating IEDs. In three patients, no IEDs were observed. These three patients (5, 7, 9) were excluded when analyzing the IED ratio.

Table 1: patient characteristics. M = male, F = female, T = temporal, Oc = Occipital, F = Frontal, C = Central, IH = interhemispheric, D = depth electrode in presumed lesion on MRI, P = Parietal, R = right, L = left

Patient #	Sex	Age (years)	location	Side	# stimulated electrode pairs	# electrodes	# electrodes with IEDs
1	M	15	T, Oc	R	45	64	8
2	F	15	F	L	55	64	19
3	F	9	F, C, IH	L	70	80	6
4	M	13	F, IH, D	L	53	62	8
5	F	41	T	L	44	64	-
6	M	14	F, D	L	43	60	13
7	M	34	T, P	L	69	96	-
8	M	22	T, C, D	L	47	54	10
9	F	18	C, D	R	58	70	-
10	M	14	C	R	56	64	8

The odds ratio for the occurrence of an evoked CCEP accompanied by power suppression when stimulating a specific stimulus pair was between 4.7 (CI: 3.0-7.4) and 11.4 (CI: 10-13) for all individual patients and 8.0 (CI: 7.5-8.5) when these patients were combined (Figure 2).

When we compared the IED ratio in response electrodes with or without evoked CCEP after stimulating a specific stimulus pair, the distributions differed significantly (Figure 3A, $p<0.01$). The absolute values and positive values of IED ratio were increased in response electrodes accompanied by an evoked CCEP (Figure 3B-C). We also observed a decrease in negative values of IED ratio in response electrodes accompanied by an evoked CCEP (Figure 3D).

When we compared the IED ratio in response electrodes with or without power suppression in the ERSP after stimulating a specific stimulus pair, the distributions differed significantly (Figure 4A, $p<0.001$). The absolute values of logarithmic IED ratio was increased when power suppression was observed in a response electrode (Figure 4B). We did not find any difference in positive values of IED ratio (Figure 4C), but we observed a decrease in negative values of IED ratio when power suppression was observed in a response electrode (Figure 4D).

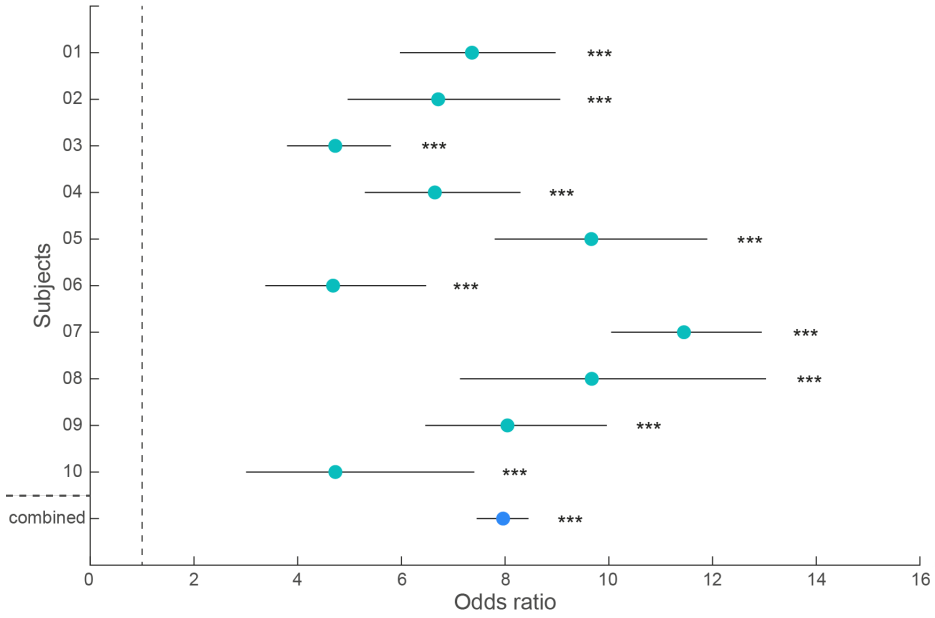


*Figure 2: The occurrence of a CCEP accompanied by power suppression in a response electrode when stimulating a specific stimulus pair is displayed for all individual patients and for all patients combined. The odds ratio varied between 4.7 (CI: 3.0-7.4) and 11.4 (CI: 10-13) in individual patients and was 8.0 (CI: 7.5-8.5) in all patients combined. *** = p<0.001, FDR corrected.*

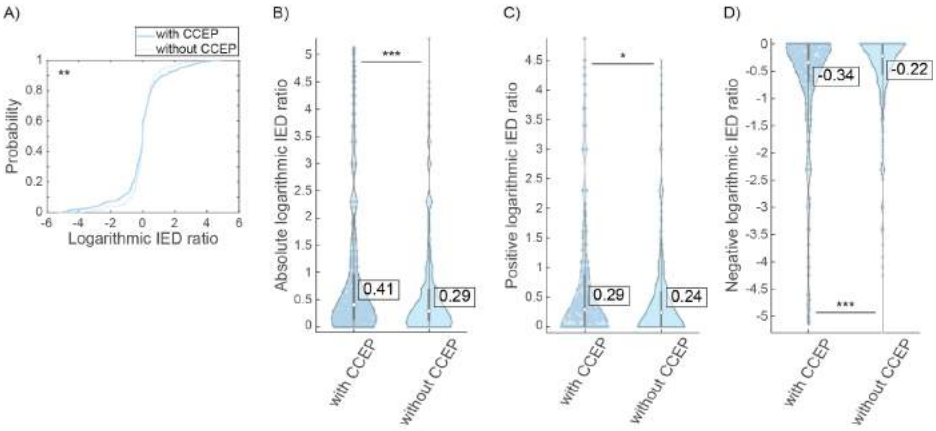


*Figure 3: Logarithmic IED ratios in response electrodes when a CCEP was (not) evoked after stimulating other electrode pairs. A) The cumulative IED ratio, showing that there was a significant difference in distributions of Logarithmic IED ratios when a CCEP was (not) evoked. B) The absolute values of logarithmic IED ratio, indicating a larger change in IEDs after stimulation when a CCEP was evoked. C) The positive values of logarithmic IED ratio, indicating a larger increase in number of IEDs after stimulation when a CCEP was evoked. D) The negative values of logarithmic IED ratio, indicating a larger decrease in number of IEDs after stimulation when a CCEP was evoked. * = p < 0.05, ** = p<0.01, *** = p<0.001, FDR corrected.*

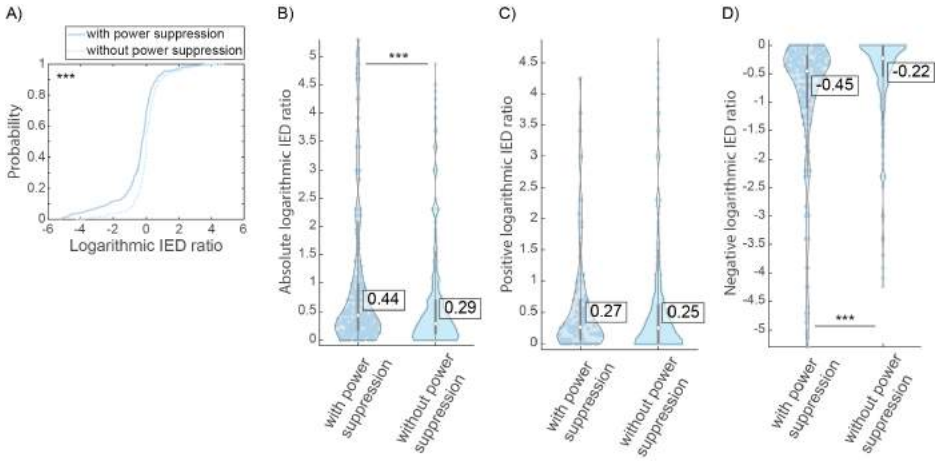


Figure 4: Logarithmic IED ratios in response electrodes when power suppression was (not) observed after stimulating other electrode pairs. *A) The cumulative IED ratio, showing that there was a significant difference in distributions of logarithmic IED ratios when power suppression was (not) observed. B) The absolute values of logarithmic IED ratio, indicating a larger change in IEDs after stimulation when power suppression was observed. C) The positive values of logarithmic IED ratio, no difference was found when power suppression was (not) observed. D) The negative values of logarithmic IED ratio, indicating a larger decrease in number of IEDs after stimulation when power suppression was observed. *** = p<0.001, FDR corrected.*

From seven subjects combined, we categorized IED electrodes after stimulating stimulus pairs into four categories: 1) with evoked CCEP and power suppression (n=169), 2) with evoked CCEP and without power suppression (n = 517), 3) without CCEP and with power suppression (n = 175), 4) without CCEP nor power suppression (n = 2741).

When we analyzed if and how long IEDs were affected by SPES stimuli (Figure 5), we observed that the numbers of IEDs were decreased post-stimulation when accompanied by power suppression and/or a CCEP (Figure 5A, C, D, G). This decrease in number of IEDs was most pronounced in electrodes that showed power suppression, regardless of the presence of a CCEP (Figure 5G, 0.2-0.4, 0.6-1, 1.2-1.4, 1.6-1.8 s post-stimulation).

We also observed an increase in number of IEDs 0.2-0.4 s and 1.2-1.4 s after stimulation when there was no power suppression and/or CCEP observed in the response electrode (Figure 5E, F, H), and when all electrodes were combined, regardless of occurrence of CCEP or power suppression (Figure 5I). In IED electrodes with a CCEP but not accompanied by power suppression, we did not see any change in number of IEDs post-stimulation (Figure 5B).

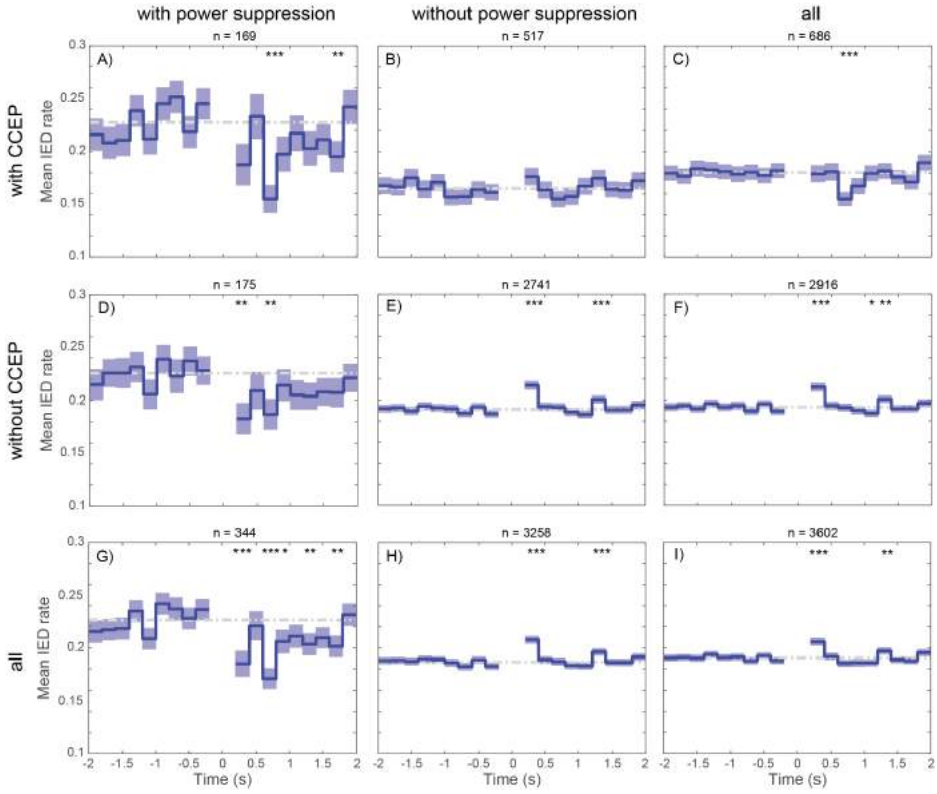


Figure 5: block signals displaying the mean number of IEDs and standard error of the mean in consecutive periods of 200 ms. *A time window of 400 ms around the stimulus artefact (t = 0 s) was excluded from analysis. Numbers of IEDs in each consecutive period of 200 ms post-stimulation were compared with the mean number of IEDs pre-stimulation (gray dotted line). A) number of IEDs when both a CCEP and power suppression were observed in the response electrode. There was a decrease in number of IEDs between 0.6-0.8 s and 1.6-1.8 s post-stimulation. B) number of IEDs when a CCEP and no power suppression was observed. There was no change in number of IEDs post-stimulation. C) number of IEDs when a CCEP was observed, regardless of the presence of power suppression. There was a decrease in number of IEDs between 0.6-0.8 s after stimulation. D) number of IEDS when power suppression and no CCEP was observed. There was a decrease in IEDs 0.2-0.4 s and 0.6-0.8 s after stimulation. E) number of IEDs when no power suppression or CCEP was observed. There was an increase in IEDs 0.2-0.4 s and 1.2-1.4 s after stimulation. F) number of IEDs when no CCEP was observed, regardless of the presence of power suppression. There was an increase in IEDs 0.2-0.4 s and 1.2-1.4 s after stimulation, but a decrease in IEDs 1.0-1.2 s after stimulation. G) number of IEDs when power suppression was observed, regardless of the presence of a CCEP. There was a decrease in IEDs 0.2-0.4 s, 0.6-1.0 s, 1.2-1.4 s and 1.6-1.8 s after stimulation. H) number of IEDs when no power suppression was observed, regardless of the presence of a CCEP. There was an increase in IEDs 0.2-0.4 s and 1.2-1.4 s after stimulation. I) number of IEDs in all electrodes, regardless of the presence of a CCEP or power suppression. There was an increase in IEDs 0.2-0.4 s and 1.2-1.4 s after stimulation. *** = p<0.001, ** = p<0.01, * = p<0.05, FDR corrected.*

Discussion

This study provides proof of principle in demonstrating that changes in brain signals are induced by SPES. We found a high association between an evoked CCEP and power suppression in ten individual patients and when these patients were combined. One study[28] showed that the stimulation response was stronger and exhibited progressive modulation in areas highly connected to the stimulation site. A few other studies [10,29,30] mentioned that cortical stimulation outside the epileptogenic region did not have any effect on IED rate. However, they did not investigate underlying effective networks [10,30], or no effective connection between the stimulus pair outside the epileptogenic region and the electrodes in the epileptogenic region was observed [29].

We found a larger absolute, positive and negative value in logarithmic IED ratios when a response electrode was connected to the stimulus pair, indicating that both an increase as well as a decrease¸ which was more pronounced, in number of IEDs could occur. Traditionally, IEDs are assumed to represent short bursts of seizure activity, but without becoming clinical seizures [31]. Another hypothesis is that IEDs increase the threshold for a seizure to occur which means that IEDs would have a protective function [32]. Whether IEDs have a facilitating or preventive function for seizures might even depend on the dynamical state of the brain [33]. The clinical implications of the two interpretations of IEDs are quite contradictory, leading to discussions whether you would like to suppress this activity with electrical stimulation. Alarcon et al. [31] found similarities in neuronal firing patterns associated with IEDs and SPES and conclude that a period of suppression in firing pattern does not result from the intrinsic properties of membranes but from the properties of the neuronal network. In the current study, we assume that both an increase and a decrease in IED rate is an indication that stimulation at a specific site has a modulating effect on epileptic activity. Further research with varying stimulus parameters in long-term electrical stimulation should give more insight in whether increase or decrease of IED rate is a good surrogate marker for effective stimulation therapy.

We also observed a decrease in IED ratio when the response electrode showed power suppression, which means that the number of IEDs after stimulation was reduced. The phenomenon of power suppression after SPES has been described in two studies [34,35]. These studies only looked at power suppression in high frequencies (>70 Hz). They both conclude that power suppression was significantly stronger in the epileptogenic tissue, but Maliia et al.[35] also found power suppression in the default mode network during 0.2-0.5 s after stimulation. Our data showed that power suppression in the response electrode would be observed more often when a direct connection, indicated

by a CCEP, between the stimulus pair and the response electrode was present. This observation was not limited to the electrodes covering epileptogenic tissue and was present when including all implanted electrodes in this analysis, suggesting that it is not a direct mathematical effect of decreased number of IEDs.

When power suppression was observed in a response electrode, a decrease in IED rate after stimulation was visible between 0.6-1.8 s after stimulation, although this was not significant during this whole period. The power suppression in ERSP plots typically occurred within a time window of 0.2-0.4 s after stimulation (Figure 1D), which means that the actual decrease in IED rate had a longer duration than was visualized in these ERSP plots. Stypulkowski et al. [37] investigated whether stimulus-induced reduction in activity was associated with reduced excitability and found that after-discharges were almost completely blocked and the amplitude of evoked potentials was reduced. Keller et al. [38] used the ratio of high-amplitude CCEPs, before versus after applying repetitive stimulation trains of 10 Hz, as a measure of cortical excitability and found that the CCEP-amplitude was modulated following repetitive stimulation. This suggests that the changes in brain signals after SPES itself, namely power suppression and the change in IED rate after stimulation, could be an interesting measure of cortical excitability. Since cortical excitability is increased for several hours before a seizure occurs [41], and many anti-epileptic drugs affect neural excitability to reduce the risk of seizures [42], the power suppression after SPES could be of importance in localizing optimal stimulation sites for effective stimulation therapy.

A striking observation was that when no power suppression or CCEP was present in an electrode, an increase in IED rate was observed between 0.2-0.4 s and 1.2-1.4 s after stimulation. Delayed responses, spikes or sharp waves occurring between 0.1-1 s after SPES [39], are represented as power increase in ERSP plots, and are a biomarker for epileptogenic tissue [25]. This increase in IEDs is found in electrodes that were not connected to the stimulus pair by a CCEP, which supports the observation that these delayed responses occur more often in indirect connections [40].

This preliminary investigation is limited to a small group of patients with heterogeneous ECoG coverage based on clinical evaluation of suspected epileptogenic tissue. It was not possible to record responses from the stimulated electrodes because of large stimulation artifacts or saturation of the amplifier that lasted for 4-5 s. Therefore, we did not have the possibility to compare responses to local stimulation in epileptogenic tissue with the observed responses to cortical network stimulation as described in this study.

Several studies [9,10] investigated whether electrical stimulation affected the IED frequency before they implanted a neurostimulator. Unfortunately, time is limited

during an intracranial monitoring period and it is not possible to test the great variety of stimulation parameter combinations in several stimulation sites. Especially in large epileptogenic regions, the optimal effect of stimulation might not be observed due to a suboptimal stimulation site, or suboptimal stimulus parameters, missing the potential that electrical stimulation might have for the specific patient. In this study, we used SPES to probe the brain in all locations covered by ECoG which gave us an indication of potential stimulation sites that might be beneficial for patient-tailored cortical stimulation therapy to reduce seizure frequency.

In conclusion, we found stimulus-induced neuromodulatory effects, by means of change in IED rate and change in spectral power, when SPES was applied in a response electrode connected to the stimulus pair. This could have a great potential to select stimulation sites for cortical network stimulation therapy.

CLOSED-LOOP CORTICAL NETWORK STIMULATION AS TREATMENT FOR REFRACTORY EPILEPSY ORIGINATING FROM THE PRIMARY MOTOR CORTEX

Closed-loop Cortical Network Stimulation as treatment for refractory epilepsy originating from the primary motor cortex

D. van Blooijs, S. Blok, E.J. Aarnoutse, N.E.C. van Klink, G.J.M. Huiskamp, M.D. Bourez-Swart, T.A. Gebbink, P. van Eijsden, P. van Rijen, S.M.A. van der Salm, N.F. Ramsey, F.S.S. Leijten

Submitted.

Abstract

Background: In epilepsy patients, cortical electrical stimulation is therapeutically applied in the seizure onset zone (SOZ) to reduce seizures. However, in patients with epilepsy arising from the primary motor cortex (M1), stimulation can result in undesired muscle contractions or loss of motor control. We postulate that seizure frequency reduction can also be obtained by cortical network stimulation in a site outside M1 with a connection to the SOZ in M1.

Methods: Patients with electroclinical seizures suspected to arise from M1 were selected. SOZ was delineated during chronic intracranial EEG monitoring. Using Single Pulse Electrical Stimulation, the underlying effective corticocortical network was determined and a site for stimulation was selected that was connected to the SOZ. One subdural strip was implanted on top of the SOZ, and one on the stimulus location. A subcutaneous neurostimulator (Activa® PC+S, Medtronic), capable of recording and closed-loop stimulation, was connected to both strips. Seizure data was collected for three to five months and used to optimize a seizure detection algorithm. After this, closed-loop cortical network stimulation was applied during seven to nine months.

Results: In five subjects (two females, mean age 34 years, range: 21-51 years), a neurostimulation system was implanted. One subject was seizure free for 17 months post-implantation without applying any electrical stimulation. Two subjects were responders with a mean seizure frequency reduction of 73%. In two subjects, seizure frequency was reduced by on average 35%.

Discussion: In this clinical trial with five subjects suffering from refractory epilepsy arising in M1, seizure frequency was reduced with electrical stimulation in all subjects. This is a proof of concept showing that closed-loop cortical network stimulation can reduce seizure frequency as equal to direct SOZ stimulation in non-primary motor epilepsy.

Disclosures: Medtronic (Minneapolis, Minnesota, United States of America) provided all components of the implant (subdural leads, extension leads, neurostimulator) and devices to set sensing and stimulation parameters (Sense Programmer, Clinician Programmer and antenna) free of charge, and provided technical support. Medtronic did not fund this study, the researchers or the patients in any other way.

Introduction

Over the last decades, neurostimulation has become a treatment option that is regularly used in refractory epilepsy patients. With deep brain stimulation and vagal nerve stimulation, large networks in the brain are modulated resulting in seizure frequency reductions of 50% in around 50% of the patients [11,20]. When there is a clear focal region responsible for epileptic seizures, more targeted, focal, cortical neurostimulation can be applied with better effects on seizure frequency reduction than large network stimulation [11]. In a few case studies [181], cortical open-loop stimulation is applied to the epileptogenic region resulting in seizure frequency reductions of around 80-90%. With open-loop stimulation, neurostimulation is applied according to a pre-programmed pattern (e.g. 1 minute on, 5 minutes off) regardless of underlying brain activity. With closed-loop stimulation, neurostimulation is applied when epileptic activity is detected. In a large trial applying closed-loop cortical neurostimulation, a responder rate of 73% and a mean seizure frequency reduction of 75% was observed [182]. In patients with epilepsy arising from the primary sensorimotor cortex, stimulation in the seizure onset zone (SOZ) may lead to side-effects like twitches or sensations [183]. Several of these cortical stimulation studies [32,184] mention that more research is needed regarding the stimulation site that is most effective for neurostimulation therapy, and that this site might not necessarily be the SOZ. We postulate that, instead of stimulating in the eloquent SOZ, stimulation in a directly connected, healthy area may be an effective alternative treatment strategy.

Recent studies [185–188] have shown that neurostimulation was more effective when the stimulation site had more connections with other regions and that the underlying network could be a predictor in effectiveness of stimulation therapy. Furthermore, we previously demonstrated[189] that single pulse electrical stimulation in a connected region modulates interictal epileptic activity in the epileptogenic area, and suggested that this might be a good indicator for long-term neurostimulation and can be used to induce seizure reduction in areas unsuited for direct cortical stimulation, most notably the primary motor cortex. In this study, we investigate whether closed loop cortical network stimulation in healthy tissue connected to the SOZ in the primary sensorimotor cortex can reduce seizure frequency and improve quality of life.

Methods

Patients

In this prospective study, we included patients who were suspected of focal epilepsy arising from the primary sensorimotor cortex around the central sulcus. Patients had

to be at least 16 years of age; with a seizure frequency of at least two seizures per day, and at least three anti-seizure medications tried.

We delineated the SOZ in detail by means of intracranial subdural EEG in order to be certain that it was indeed located within the primary sensorimotor cortex and was not eligible for surgery because of the risk of unacceptable functional deficits post-surgery. Candidates in whom this criterium was not met, underwent epilepsy surgery and were then excluded from the neuromodulation trial.

The REC2Stim (Rational Extra-eloquent Closed-loop Cortical Stimulation) study was approved by the ethics committee at the University Medical Center Utrecht and the national Dutch Health and Youth Care Inspectorate, in accordance with the Declaration of Helsinki (2013). This study was registered with clinicaltrials.gov (NCT04158531).

Informed consent procedure

People were aware of, and conditionally assented to, alternative neuromodulation treatment in case the clinical invasive monitoring would reveal a non-resectable focus in the primary sensorimotor cortex. They were given full information on the REC2Stim neuromodulation trial, including its experimental part. Patients signed an intention to informed consent before undergoing invasive epilepsy monitoring, which technically counted towards study participation. Final informed consent was obtained only after clinical delineation of the SOZ in eloquent cortex. This approach was adopted because confronting the patient with the trial at the end of a clinical invasive epilepsy monitoring period would leave insufficient time for considerations and questions.

Invasive epilepsy monitoring

Patients underwent clinical invasive epilepsy monitoring with subdural electrocorticography (ECoG) for 4-7 days. During implantation surgery, a trepanation was performed and electrode grids were placed subdurally over the pericentral area suspected of generating seizure activity. This area was determined with pre-surgical evaluation, including seizure semiology, MRI and video-EEG.

During this invasive epilepsy monitoring period, we visually analyzed spontaneously occurring seizures to delineate the SOZ, and applied electrical stimulation mapping to delineate motor and sensory functions. We applied Single Pulse Electrical Stimulation (SPES; ten monophasic, bipolar stimuli of 0.2 Hz, 4-8 mA, 1 ms) to each neighboring electrode pair. In our hospital, SPES is used as part of the clinical evaluation to localize the epileptogenic region [60]. We reconstructed the underlying effective network [89] from the corticocortical evoked potentials (CCEPs) to SPES stimuli. In this network,

we determined electrodes outside the eloquent region with connections towards the SOZ, and determined whether SPES stimuli in these extra-eloquent electrodes resulted in transient suppressive effects in the ongoing ECoG inside the SOZ. Electrode sites connected to the epileptogenic region and modulating activity in the SOZ on SPES stimulation were potential candidates for therapeutic stimulation after completion of invasive epilepsy monitoring. Details of this procedure are provided in the Supplementary Appendix and Supplementary figure 1.

Selection of electrodes for seizure detection

Consensus between the responsible neurologist (FL) and the clinical neurophysiology team specified the SOZ electrodes based on visual inspection of the seizure data. We analyzed their interictal and ictal power spectrum. The electrodes that showed the largest difference between interictal and ictal power spectra were selected as the sensing site for seizure detection. Details of the electrode selection for seizure detection are provided in the Supplementary Appendix and Supplementary figure 2.

Selection of electrodes for therapeutic stimulation

Based on their connection to the SOZ and neuromodulatory effects during SPES (see Supplementary Appendix and Supplementary figure 1), we selected three potential candidate sites in each patient for stimulation trials with various frequencies and current intensities during two days prior to grid explantation and implantation of the neurostimulator. We analyzed power spectra pre- and post-stimulation and determined the most effective of the three locations for therapeutic neurostimulation. Details of the stimulation protocol and of the electrode selection for therapeutic stimulation are provided in the Supplementary Appendix, Supplementary figure 3, and Supplementary figure 4.

Implantation and description of the neurostimulation device

For this study, a neurostimulator (Implantable Pulse Generator, Activa PC+S®, Medtronic) with sensing capabilities was used. The Activa® PC+S is an investigational device provided by Medtronic for use in clinical research studies. All components of this device, including electrode leads, were designated for investigational use. Details of the features of the neurostimulator are provided in the Supplementary Appendix and Supplementary figure 5. The neurostimulator was connected to two subdural electrode strips (Subdural leads, Medtronic; electrode diameter 4 mm, interelectrode distance 1 cm, 4 electrodes per lead) approved for both recording and stimulation. Positioning on target location was guided by neuronavigation. During

the clinical implantation surgery, four burr holes had been made in the trepanation margin approximating a rectangle acting as a neuronavigation reference. Location of the sensing and stimulation electrode strips were marked on the cortex with a marking pen (type 1041, SandelMedical) and the neuronavigation wand. Both subdural strips were fixated to the cortex with Tisseel and each lead was sutured to the dura. During closure of the dura, the strips were fixated to the dura with sutures after verification of the correct location with the neuronavigation wand.

Extension leads were connected to the electrode strip leads, tunneled subcutaneously and connected to the neurostimulator that was placed subcutaneously beneath the clavicle. The patients were discharged from the hospital 2-4 days after implantation of the neurostimulator.

Data collection phase

During three months after implantation, we asked the patients to initiate a recording of seizure data in time domain format when they experienced a seizure (see Supplementary Appendix and Supplementary figure 5) and to simultaneously keep a seizure diary. During each research visit (one visit per two weeks), the ECoG data was exported from the neurostimulator. This data was analyzed to select frequency bands that changed significantly when pre-ictal ECoG signals changed towards the ictal state. The device was then programmed to record power domain data simultaneously with time domain data to affirm that a detectable change in power was observed during seizure onset. From this power domain data, a linear discriminant algorithm (LDA) was constructed to distinguish seizure onset activity from interictal activity. This LDA was then tested and tuned until a sensitivity of > 50% and a false detection rate of < 20/hour was reached. We then continued to the next phase in which cortical stimulation is initiated when a seizure is detected. Details of the calculation of the LDA are provided in the Supplementary Appendix and Supplementary figure 6.

Closed-loop cortical stimulation phase

After the data collection phase, the patient was asked to continue recording seizures to verify the performance of the LDA detector and to keep a seizure diary. The patient visited the hospital once per month. For nine months, we optimized stimulation parameters to reduce seizure frequency. We compared the seizure frequency in month 11-12 with the seizure frequency during the data collection phase. Statistical analysis was performed with the Mann-Whitney U test ($p<0.05$).

Quality of life, sensorimotor function and participation in society

One day before the start of the clinical monitoring period, and one year after inclusion in this study, the patient completed two questionnaires regarding the quality of life (aQoL-8D) and participation in society (USER-test). We also tested motor hand function with the Action Reach Arm Test (ARAT), the nine-hole peg test, and performed physical examination.

Results

Subjects

We included seven subjects in this study between November 2019 and November 2020 (see Table 1 for subject characteristics, and Figure 1 for a timeline). In two subjects (REC2Stim02 and REC2Stim04), the SOZ turned out to be located outside essential eloquent cortex, so these subjects underwent epilepsy surgery and were excluded from this study. The other five subjects (REC2Stim01, REC2Stim03, REC2Stim05, REC2Stim06, REC2Stim07) proceeded with implantation of the neurostimulator. Additional details regarding the exact implantation location of the subdural electrodes is provided in the Supplementary Appendix and Supplementary figure 7.

Table 1: subject characteristics. REC2Stim02 and REC2Stim04 were excluded from this study, since the SOZ was located outside the primary sensorimotor cortex and epilepsy surgery was performed. F = female, M = male, R = right, L = left

Subject	Age (years)	Sex	Affected side	Involved extremity	Resection/neurostimulator
REC2Stim01	38	F	R	Hand	Neurostimulator
REC2Stim02	21	F	R	Hand	Resection
REC2Stim03	23	M	R	Leg	Neurostimulator
REC2Stim04	50	F	L	Mouth	Resection
REC2Stim05	24	M	L	Leg	Neurostimulator
REC2Stim06	51	F	R	Leg	Neurostimulator
REC2Stim07	33	M	L	Hand	Neurostimulator

Subjects who underwent epilepsy surgery

In REC2Stim02, we delineated the SOZ outside the primary sensorimotor hand area. The SOZ was located in the frontal cortex with fast spreading into the primary sensorimotor cortex. She underwent cortectomy in the posterior frontal lobe, anterior of the precentral sulcus. Pathology of the resected tissue showed a Focal Cortical Dysplasia (FCD) 2B. A year after surgery, she remains seizure free and will start tapering off anti-seizure medication.

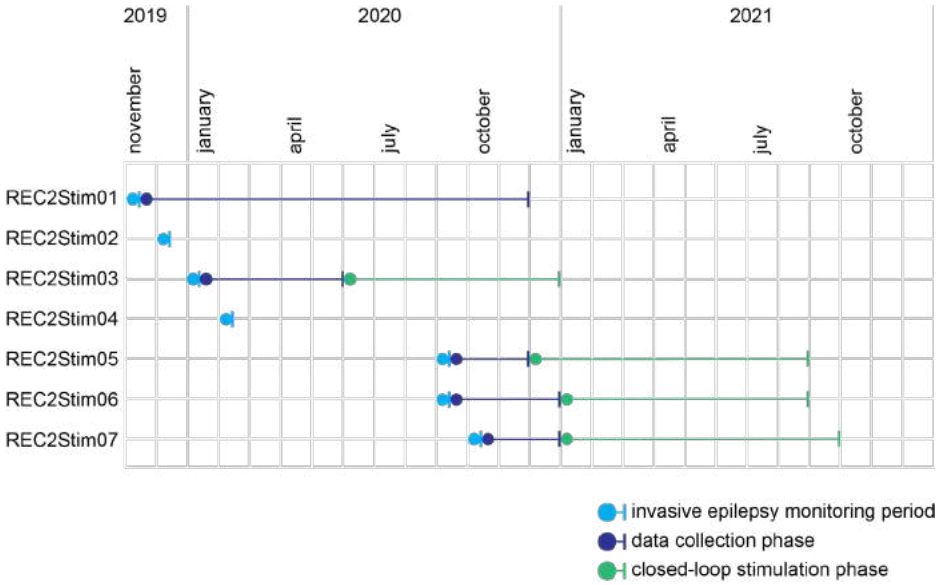


Figure 1: Timeline of study participation for each subject. *The first subject was included in November 2019. The last subject was included in October 2020. Two subjects (REC2Stim02 and REC2Stim04) were excluded from this study during the invasive epilepsy monitoring period (light blue), since epilepsy surgery was performed. Five subjects underwent invasive epilepsy monitoring (light blue), implantation of the neurostimulator, after which the data collection phase (dark blue) and the closed-loop stimulation phase (green) followed. Study participation of the last subject ended in October 2021.*

In REC2Stim04, an abnormally large sensorimotor mouth representation was found in the ventral precentral gyrus. The large FCD 2B, already visible on MRI, was localized in this area and deemed resectable. One year after surgery, she still had seizures and she underwent a second resection for residual FCD on MRI. Currently, she is not completely seizure free, but the final result is entirely satisfactory for her; she went from seven seizures per night to one very short seizure a week, lasting a few seconds, on awakening.

Data collection phase

Following the implantation of the neurostimulator, REC2Stim01 ceased to have her regular seizures, though she reported some erratic twitches in her hand. This was insufficient to optimize a seizure detection algorithm and apply closed-loop cortical stimulation. The other four subjects went on to participate in the data collection phase and stimulation phase. During the data collection phase, we recorded on average 281 (range: 115-743) seizures per subject in the remaining four subjects. The performance of the LDA to detect seizures had a sensitivity of 70-95% and a false detection rate of 1-5/hour.

Additional details regarding the performance are provided in Supplementary Appendix and Supplementary figure 8.

Seizure frequency

In the last two months of the stimulation phase, the seizure frequency was reduced by 70%, 77%, 26% and 44% in REC2Stim03, REC2Stim05, REC2Stim06 and REC2Stim07 respectively, as compared to the seizure frequency during the data collection phase (see Figure 2). This reduction was significant in two subjects (REC2Stim03 and REC2Stim05, $p<0.001$).

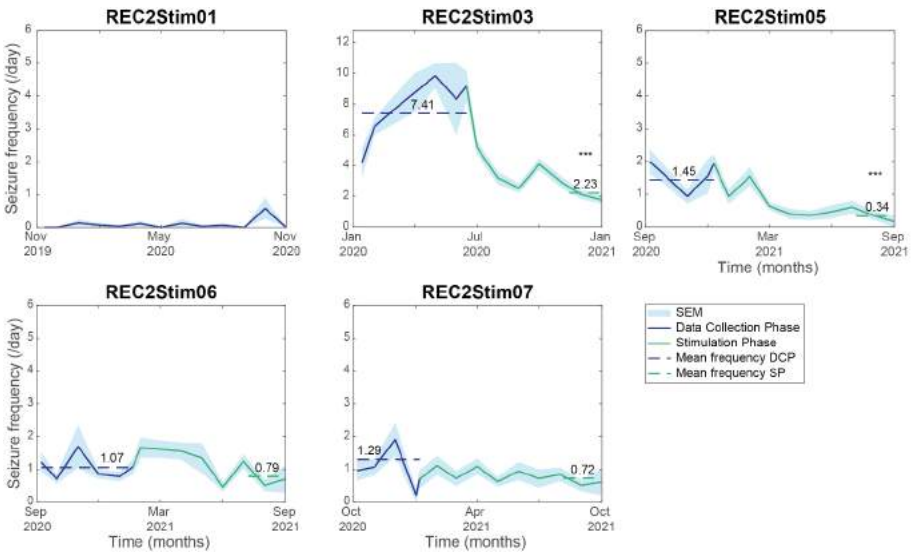


*Figure 2: The mean seizure frequency during the data collection phase (DCP, dark blue), during the closed-loop cortical stimulation phase (SP, green) and the standard error of the mean (SEM, light blue) are displayed. The mean seizure frequency during the last two months of the SP (dotted green line) was significantly lower in subjects REC2Stim03 and REC2Stim05 compared to the mean seizure frequency during the DCP (dotted dark blue line). Note that the y-scale of REC2Stim03 has higher limits than the y-scales of the other patients. ***: p<0.001*

Quality of life, participation in society and sensorimotor function

We did not find a clear difference between quality of life before implantation of the neurostimulator and a year after study participation (see Figure 3A). In REC2Stim01 and REC2Stim06, the self-reported ability to participate in society was increased a year after study participation (see Figure 3B). In the other subjects, we did not find a clear difference. Regarding functioning of the hand (see Figure 3C&D), we did not find a clear difference. Although we did not find any differences in quality of

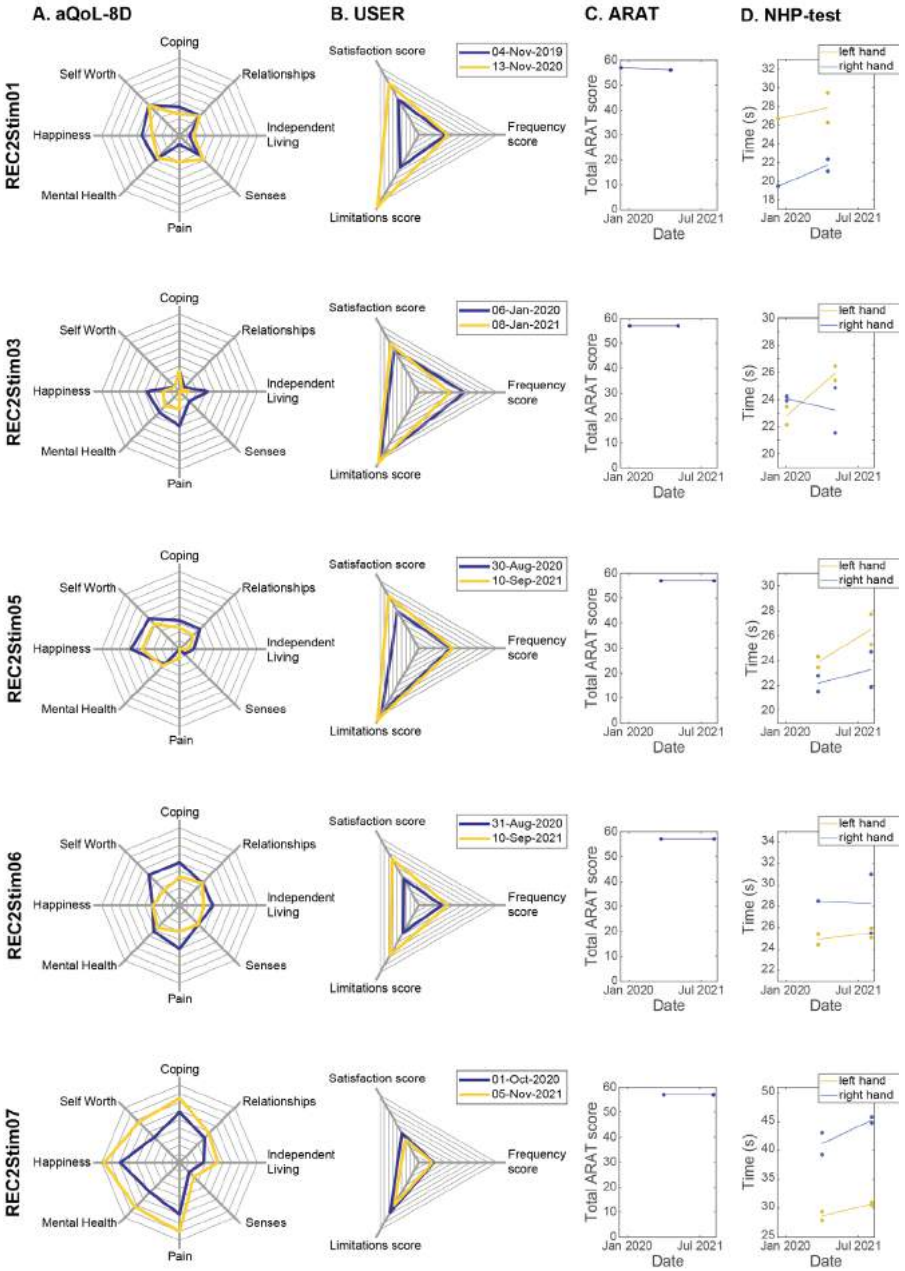


Figure 3: For five subjects, the quality of life, measured with the aQoL-8D (A) and the level of participation in society, measured with the USER test (B) are displayed prior to implantation of the neurostimulator (dark blue) and a year after study participation (yellow). Motor hand function, measured with the ARAT (C) and the nine-hole peg test (D), are displayed prior to implantation of the neurostimulator and a year after study participation.

life or ability to participate in society, we observed some individual improvements. In REC2Stim06, one anti-seizure medication was stopped because of side-effects. This did not lead to an increase of seizures. Both REC2Stim06 and REC2Stim07 had a history of yearly admissions to the hospital because of a cluster of uncontrollable seizures. This did not occur during participation in this early feasibility study. All participants expressed that they would like to continue with the closed-loop cortical network stimulation treatment after the end of study participation.

Complications

REC2Stim01 reported a headache a week after implantation of the neurostimulator. This resolved in three weeks. She also reported a tingling sensation in the left side of her tongue when she was tired. Two months later, this was resolved without intervention.

REC2Stim03 had an increase of seizure frequency (normally 1 tonic-clonic seizure per 2 weeks, and after implantation 1-4 tonic-clonic seizures every night) during a week after implantation of the neurostimulator. Clobazam was given for one week, and the seizure frequency decreased to baseline afterwards.

When we started the closed-loop cortical network stimulation, REC2Stim05 reported seizures during the day, while he was only familiar with nocturnal seizures. We resolved this by switching off the neurostimulator during the day. No other adverse events were reported.

Other relevant findings after one year follow-up

After one year of follow-up, some relevant findings and technical complications occurred. These findings are discussed in detail in the Supplementary Appendix.

Discussion

We implanted a neurostimulator in five subjects with refractory epilepsy arising from the primary sensorimotor cortex. One subject became seizure-free after only implanting the neurostimulator without applying any electrical stimulation. She had a presurgical high burden of regular seizures and had shown 80 seizures in six days of invasive monitoring just before. This surprising effect might be mediated by the expectation of the clinical benefit to be obtained, as was described in a study investigating placebo effect during deep brain stimulation treatment in patients with Parkinson's disease [190]. In the other four subjects, we were able to detect seizures with a sensitivity of at least 70% and a false detection rate of <5 /hour. Two subjects responded to closed-loop cortical network stimulation with a mean seizure frequency reduction of 73%. The two other subjects had a mean reduction

of 35%. In another study applying responsive neurostimulation, the median seizure frequency reduction was 44% after one year [22]. This reduction increased to 53% after two years and 75% after nine years [182]. This suggests that underlying network excitability changes due to the applied neurostimulation and efficacy increases over the years. In the next few years, we will be able to evaluate whether this effect is also present in the subjects that participated in our study.

In this clinical early feasibility study, we included seven subjects suspected of focal epilepsy arising from the primary sensorimotor cortex with low odds of proceeding towards epilepsy surgery. During presurgical evaluation with subdural electrode grids covering the presumed epileptogenic regions, we concluded that epilepsy surgery was possible in two subjects (almost 30%). Prior to this study, the odds for epilepsy surgery was estimated at <10%, and clinical invasive monitoring would likely not have been done. Our study shows that epilepsy surgery might be feasible in more patients with a suspected focus in the primary sensorimotor cortex. In a study of the subjective effects of responsive neurostimulation [191], quality of life improved in 44% of the patients. Interestingly, these findings were not explained by changes in seizure frequency or anti-seizure medication. We did not see clear differences in quality of life pre-implantation and a year after. Our study was executed between November 2019 and November 2021. Around the same time, covid-19 impacted our daily lives. This might have influenced the quality of life ratings and ability to participate in society for our subjects. Furthermore, improvement in quality of life continues to be observed throughout a follow-up duration longer than one year [192].

We did not find any differences with physical examination one year after study participation compared to prior to implantation of the neurostimulator. We did not observe any differences in motor hand function due to stimulation. When setting up this trial, we expected the majority of eligible patients to have involvement of the sensorimotor hand region. In the end, three of our subjects had seizures arising from motor leg/foot area. One of the two implanted subjects with seizures arising from the motor hand area did not receive stimulation due to the absence of seizures since implantation (REC2Stim01), leaving only one subject to evaluate.

In this study, we applied closed-loop stimulation. In a large trial on responsive neurostimulation [22] with similar results on seizure frequency reduction, electrical stimulation was applied upon seizure detection with a burst duration of 100 ms and a total stimulation duration of 5.9 min/day, leading to a stimulation every 30 s. This suggests that not only ictal activity, but also interictal activity was detected and responded to with electrical stimulation. The question remains what is better:

closed-loop stimulation, stimulation applied on both interictal and ictal activity or stimulation applied in an open-loop cycle. Some studies demonstrated reduced spike-wave-discharges in a genetic absence model in rats[193] or suppression of seizure-like activity in hippocampal brain slices [194] with closed-loop stimulation that were not observed with open-loop stimulation, while high efficacy with open-loop stimulation has been demonstrated in case studies as well [25,30]. One of the advantages of closed-loop stimulation is the minimization of side effects related to stimulation when there are no seizures [9]. Furthermore, closed-loop stimulation minimizes power consumption and delivers a lower total daily dose of current, which both benefits battery life of the neurostimulator [9].

In clinical practice, treatment efficacy is commonly evaluated based on seizure diaries reported by the patient. In this study, we also relied on these self-reported seizure diaries. The seizure frequency derived from these self-reports is usually inaccurate, and does not include subclinical events [9], which is a general concern when evaluating treatment efficacy. Additionally to the seizure diary, subjects used a Patient Programmer (see Supplementary Appendix and Supplementary figure 5 for properties of the neurostimulator) that logged ictal events in the neurostimulator. This might produce a more reliable diary than a traditional self-reported one [195].

During intracranial monitoring, we performed some extra stimulation trials in which we applied several stimulation frequencies and analyzed the effect in the SOZ in order to determine the stimulation site with best modulating effect on seizure activity. When starting the closed-loop cortical network stimulation phase, we selected our first stimulation frequency based on the responses to stimulation during the extra stimulation trials. We hoped that spectral changes in interictal activity due to stimulation would be a predictor for long-term neuromodulatory effects. However, in this small set of subjects, we were not able to find a clear relationship between the responses to stimulation in the extra stimulation trials during the intracranial monitoring and long-term effect on seizure frequency. This means that more research is needed to find predictors for effective stimulus parameters in the individual subject. This could minimize the long trajectory of trial-and-error with stimulus parameters that is now often clinical practice for patients with epilepsy receiving neuromodulation therapy.

In this clinical early feasibility study, we have demonstrated that closed-loop cortical network stimulation in an area of healthy tissue connected to the SOZ led to a mean seizure frequency reduction of 54%. In the following years, we will continue applying stimulation with different stimulation paradigms to improve the treatment with optimized seizure frequency reduction.

Supplementary Appendix

Invasive epilepsy monitoring period – Electrical stimulation mapping

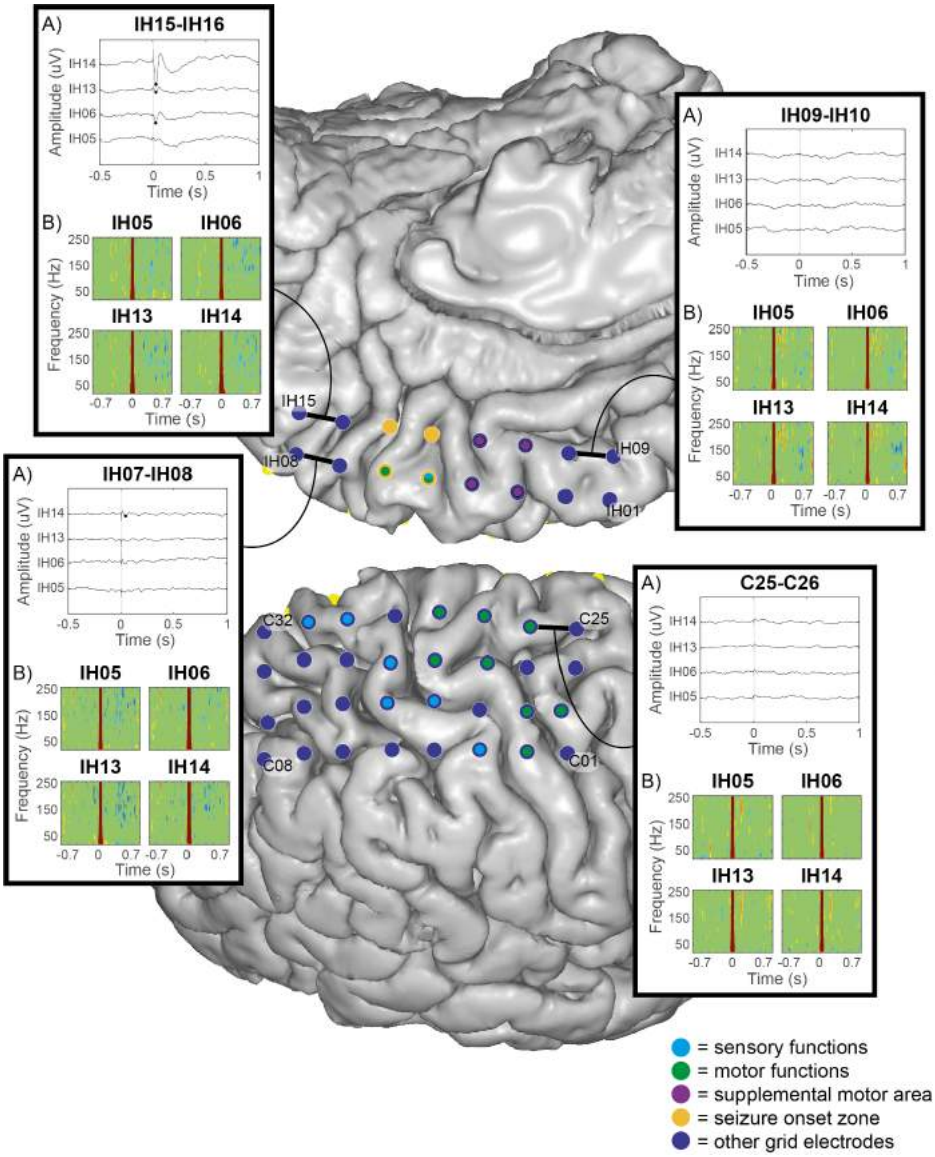
We applied electrical stimulation mapping (50 Hz, 1-6 mA, 1025 μs, biphasic, for 1-5 s) in each neighboring electrode pair. When the patient would experience symptoms like twitches, sensations or an epileptic aura, this electrode pair would be noted as involved with this specific function or with evoking seizures. After applying stimuli to each pair, we reconstructed a map that showed which areas were involved in which function and/or epileptic aura. This map facilitated delineation of regions that were suitable or unsuitable for resection, optimizing the chances of seizure freedom while minimizing the risk of neurological deficits (see Supplementary figure 1).

Invasive epilepsy monitoring period – Single Pulse Electrical Stimulation

We applied Single Pulse Electrical Stimulation (SPES; ten monophasic, bipolar stimuli of 0.2 Hz, 4-8 mA, 1 ms) to each adjacent electrode pair (SD LTM STIM Cortical Stimulator, Micromed, Treviso, Italy). For each stimulus pair, we selected epochs of the data time-locked to the stimulus artefact in a time window of 2 s before until 2 s after each stimulation for each response electrode.

First, we analyzed the underlying cortico-cortical network by evaluating the Cortico-Cortical Evoked Potentials (CCEPs, see Supplementary figure 1A). We averaged the epochs during ten trials per stimulus pair. In the averaged signal, a CCEP was detected when the signal exceeded 2.6 * standard deviation, which was calculated in the time window of 1 – 0.1 s prior to the stimulus artefact. All detected CCEPs were visually checked (DvB) to reduce false-positive detections.

Secondly, we analyzed which Single Pulse Stimuli modulated the SOZ by evaluating transient power reduction post-stimulation. After making epochs as described earlier, we calculated event-related spectral perturbations (ERSP [196]) with a 3-cycle wavelet with a Hanning-tapered window in which the number of cycles increases with 20% between the frequency range of 10-250 Hz. Bootstrapping was applied to display only significant differences ($p < 0.05$) in power post-stimulus compared to pre-stimulus (see Supplementary figure 1B).



Supplementary figure 1: Intracranial grid implantation of REC2Stim03. With electrical stimulation mapping, we delineated sensory (light blue), motor functions (green) or supplemental motor area (purple). The seizure onset zone (SOZ, yellow) was delineated based on seizures that occurred during the invasive epilepsy monitoring period. With SPES, we reconstructed connections towards the SOZ. In the upper left box, stimulation in electrodes IH15-IH16 showed a CCEP (A) in response electrodes IH6, IH13, IH14. The time-frequency plots (B) display changes in power in electrodes IH05, IH06, IH13, IH14 after stimulating IH15-16 (upper left box), IH07-IH08 (lower left), IH09-IH10 (upper right) and C25-C26 (lower right). We did not observe any CCEPs or transient power suppression in electrodes IH05, IH06, IH13, IH14 when stimulating electrode pair C25-C25. We observed either CCEPs or transient power suppression in IH05, IH06, IH13, IH14 when stimulating any of the other three electrode pairs.

Selection of seizure detection site

Seizures were visually annotated by the responsible neurologist (FL) and the clinical neurophysiology team. We selected epochs with a time window of 30 s pre-seizure to 30 s after seizure onset of all seizures that occurred spontaneously during the invasive epilepsy monitoring period. We applied a notch filter (Butterworth, 3rd order, 47-53 Hz and 97-103 Hz) to remove 50 Hz and 100 Hz line noise. We applied a Gabor wavelet convolution and calculated the power in the frequency bands 4-7 Hz, 8-14 Hz, 15-25 Hz, 26-40 Hz and 65-95 Hz in a time window of 15 s pre-seizure and 5 s during seizure onset. We averaged the power in each frequency band over all samples pre-seizure and during seizure onset and tested statistical significance between the power pre-seizure and during seizure onset in each frequency band in each electrode with a Wilcoxon signed rank test ($p < 0.05$). We applied FDR correction to correct for multiple testing (see Supplementary figure 2). The electrodes that showed the largest difference between interictal and ictal power spectra were selected as the sensing site for seizure detection.

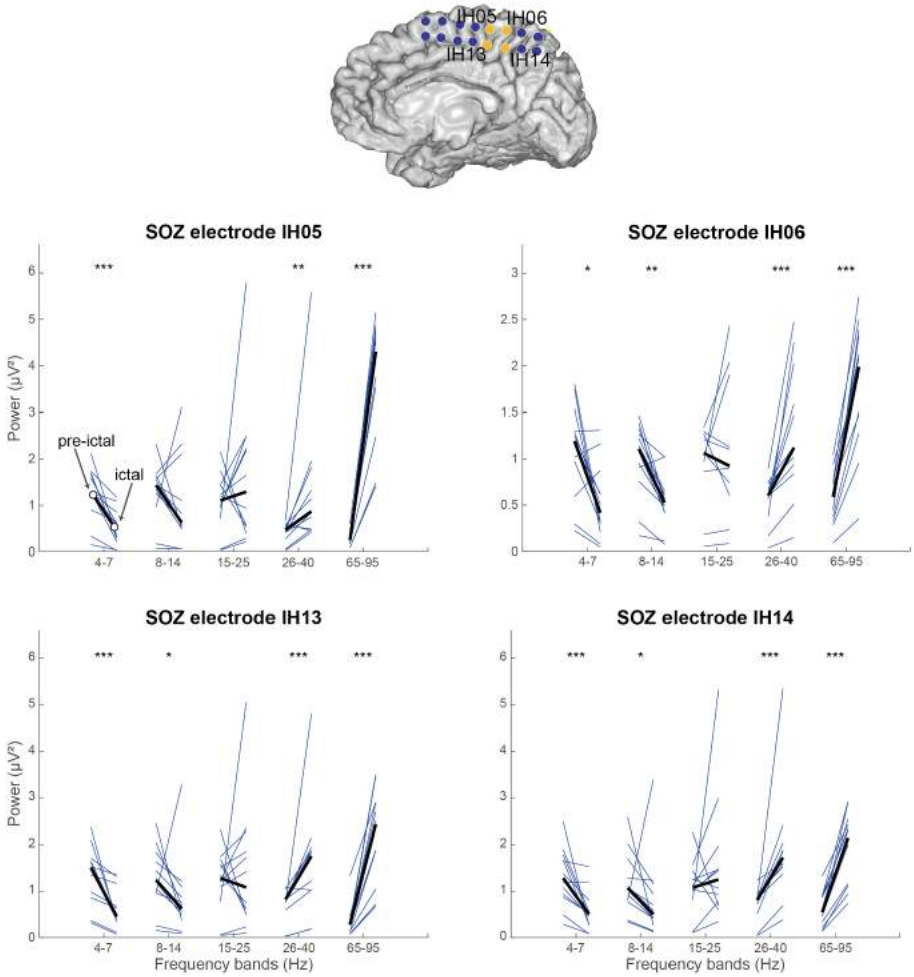
Selection of electrodes for therapeutic stimulation

We selected three potential candidates for extra stimulation trials based on whether the potential stimulus sites evoked a CCEP in the SOZ and whether we observed transient power suppression in the SOZ after SPES stimulation (see Supplementary figure 1 for more details).

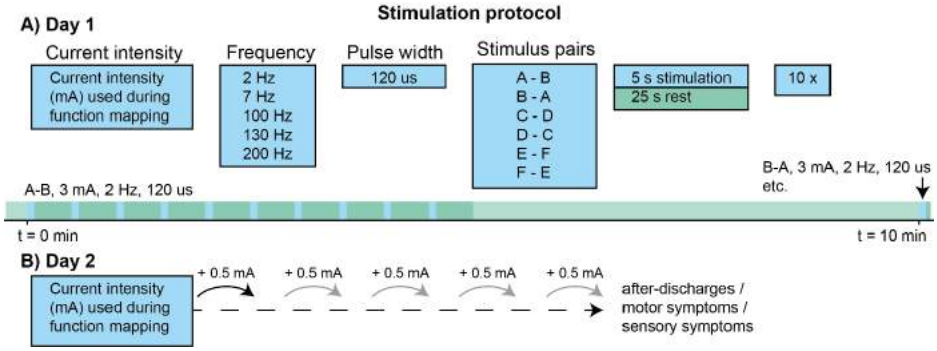
We applied runs of ten stimuli (5 s of stimulation, 25 s rest) at the current intensity that did not evoke after-discharges (3-15 mA) during electrical stimulation mapping, and a pulse width of 120 μs at various stimulation frequencies (2, 7, 100, 130, 200 Hz). After each set of ten stimuli, we paused for ten minutes and continued with the next set of ten stimuli. In total, this protocol took five hours (see Supplementary figure 3A). Due to limited time in this invasive epilepsy monitoring period, we could only select three potential stimulation candidates.

One day prior to the implantation of the neurostimulator, we increased the current intensity in the selected stimulation site with steps of 0.5 mA to see what current intensity would lead to clinical symptoms or after-discharges (see Supplementary figure 3B).

During this epilepsy monitoring period, we had to analyze effects of stimulation trials on interictal data. Due to the limited time, it was not possible to analyze effects of these various stimulation trials on ictal data.



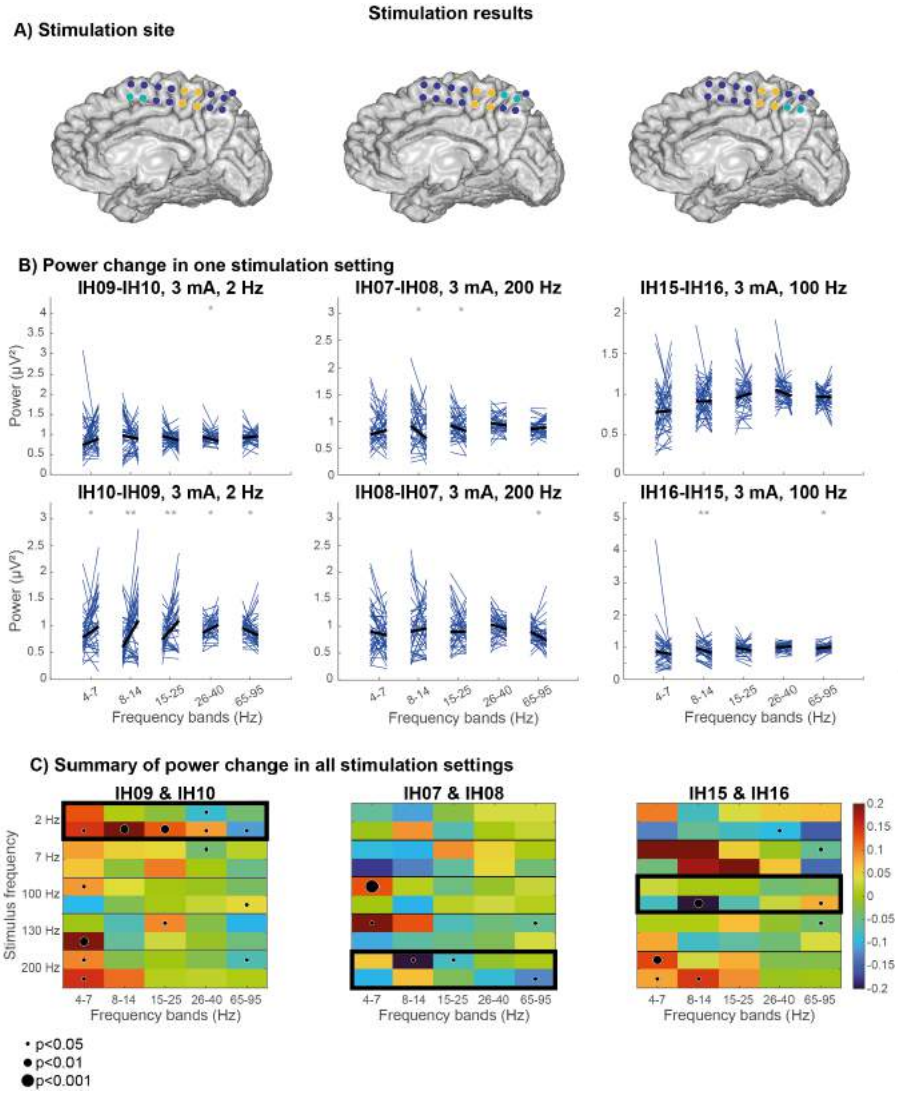
*Supplementary figure 2: Selection of electrodes for seizure detection in REC2Stim03. In each frequency band, the power in pre-ictal (left) and ictal (right) epochs are displayed. In all electrodes defined as covering SOZ, we observe that there is a power increase in 26-40 Hz and 65-95 Hz during ictal activity. Power is decreased in 4-7 Hz frequency band during ictal activity. In all electrodes except IH05, a decrease in power in 8-14 Hz frequency band was also observed during ictal activity. *: p<0.05, **: p<0.01, ***: p<0.001 (FDR corrected).*



Supplementary figure 3: The stimulation protocol was executed on two consecutive days. A) On the first day, ten stimulation trials with various stimulation frequencies were applied in three stimulation sites. B) On the second day, current intensity was increased with iterative steps of 0.5 mA to determine the potential range of stimulation without functional effects or evoking after-discharges.

Data was recorded with a sample frequency of 2048 Hz. We re-referenced the data with a common average. The electrodes in which artefacts or 50 Hz line noise was observed, were excluded in this common average. We also applied stimulus artefact removal with the following method. We calculated the average of the signal at two sample points: 10 samples before stimulus onset and 30 samples after stimulus offset and replaced the data with this average value in a time window of stimulus onset until 20 samples after stimulus offset. The stimulus artefact would otherwise leak into the epochs that we wanted to analyze. We then applied a notch filter (Butterworth, 3rd order, 47-53 Hz and 97-103 Hz) to remove 50 Hz and 100 Hz line noise.

We selected epochs of 45 s pre-stimulation and 45 s post-stimulation, applied a Gabor wavelet convolution and calculated the power in the frequency bands 4-7 Hz, 8-14 Hz, 15-25 Hz, 26-40 Hz and 65-95 Hz in a time window of 11-1 s pre-stimulation and 1-11 s post-stimulation. We averaged the power in each frequency band over all samples pre- and post-stimulation and tested statistical significance between the power pre- and post-stimulation in each frequency band for each stimulation parameter with a Wilcoxon signed rank test ($p<0.05$). We applied FDR correction to correct for multiple testing (see Supplementary figure 4). Based on the effect of applying stimuli in the three stimulation pair candidates, we determined which site would be most promising for long-term therapeutic stimulation.

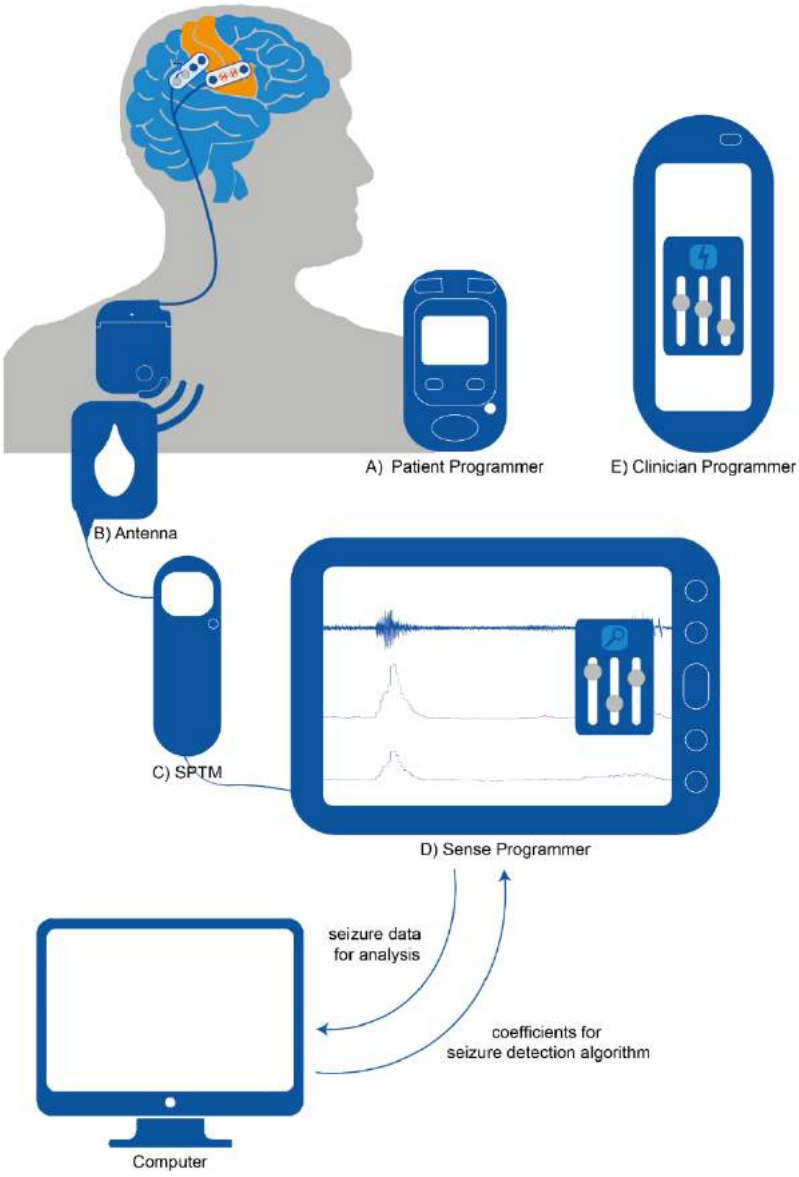


*Supplementary figure 4: Selection of electrodes for therapeutic stimulation. A) In yellow, the electrodes in the seizure onset zone were indicated. In light blue, the stimulation site is indicated. In purple, all other intracranial electrodes are indicated. B) For each stimulation site, the effect of one set of stimulation parameters is displayed for five frequency bands of the response electrodes located in the seizure onset zone. **: p<0.01, *: p<0.05 (no FDR correction, since this would remove all significant differences). C) A summary of power change in all stimulation settings. For each stimulus frequency, the two polarities of stimulation are shown (e.g. IH09-IH10 and IH10-IH09). The thick box around one stimulation frequency indicates which example was shown in B.*

Features of the Implantable Pulse Generator (Activa® PC+S)

The Activa® PC+S is able to record data in three modes: 1) at a specific moment in time (e.g. every 6 hours), 2) when a patient initiates a recording by pushing a button on the Patient Programmer, 3) when a certain event is detected. In 2) and 3), data is continuously recorded in a buffer and can be stored before and after the Patient Programmer is used or an event is detected. Thus, when initiating a recording when the patient experiences a seizure, data is also stored during a few seconds prior to the use of the Patient Programmer. During the data collection phase, we asked a patient to initiate a recording by using the Patient Programmer (see Supplementary figure 5A). We also recorded interictal data according to a time schedule. A log-file is made automatically in the Activa® PC+S to track all detections, time triggered data recordings and Patient Markers. During a research visit, both the recorded data and this log-file were exported from the Activa® PC+S to the Sense Programmer (see Supplementary figure 5D) via an antenna and SPTM (see Supplementary figure 5B and 5C), after which the data was transferred to an external computer. The seizure data and interictal data was used to optimize the seizure detection algorithm. Coefficients of this detection algorithm were transferred back to the Sense Programmer and implemented in the Activa® PC+S.

The Clinician Programmer (see Supplementary figure 5E) was used to evaluate the battery level and impedances in the electrodes. During the cortical closed-loop stimulation period, the Clinician Programmer was used to set stimulation parameters.

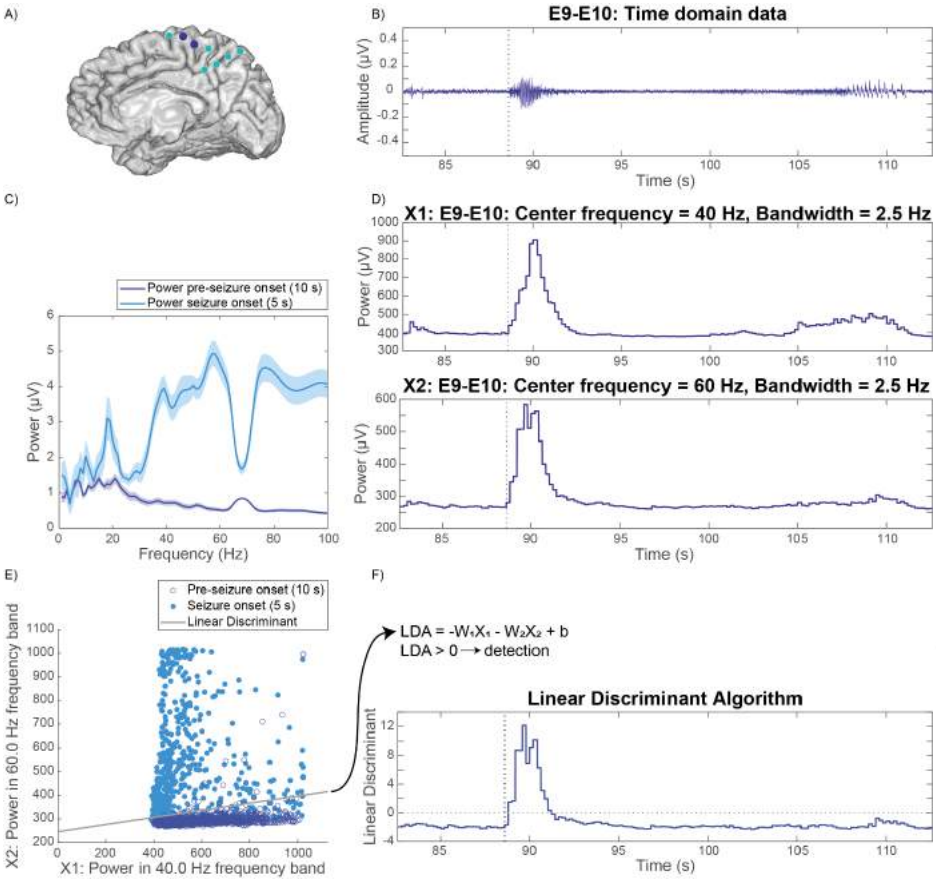


Supplementary figure 5: components of the neurostimulation system. *The subdural electrodes are placed on top of the SOZ in the primary sensorimotor cortex (orange) and on a stimulation site outside this eloquent area. These electrodes are connected to the Activa® PC+S via extension leads. The patient initiates a recording by pushing a button on the Patient Programmer (A). During a visit at the outpatient clinic, the antenna (B) is placed on top of the neurostimulator and connected to the Sense Programmer (D) via the SPTM (C). The Sense Programmer is used to visualize the recordings, change sensing settings and implement the coefficients for the seizure detection algorithm. The Clinician Programmer (E) is used to check battery level and impedances of the electrodes, and set stimulus parameters.*

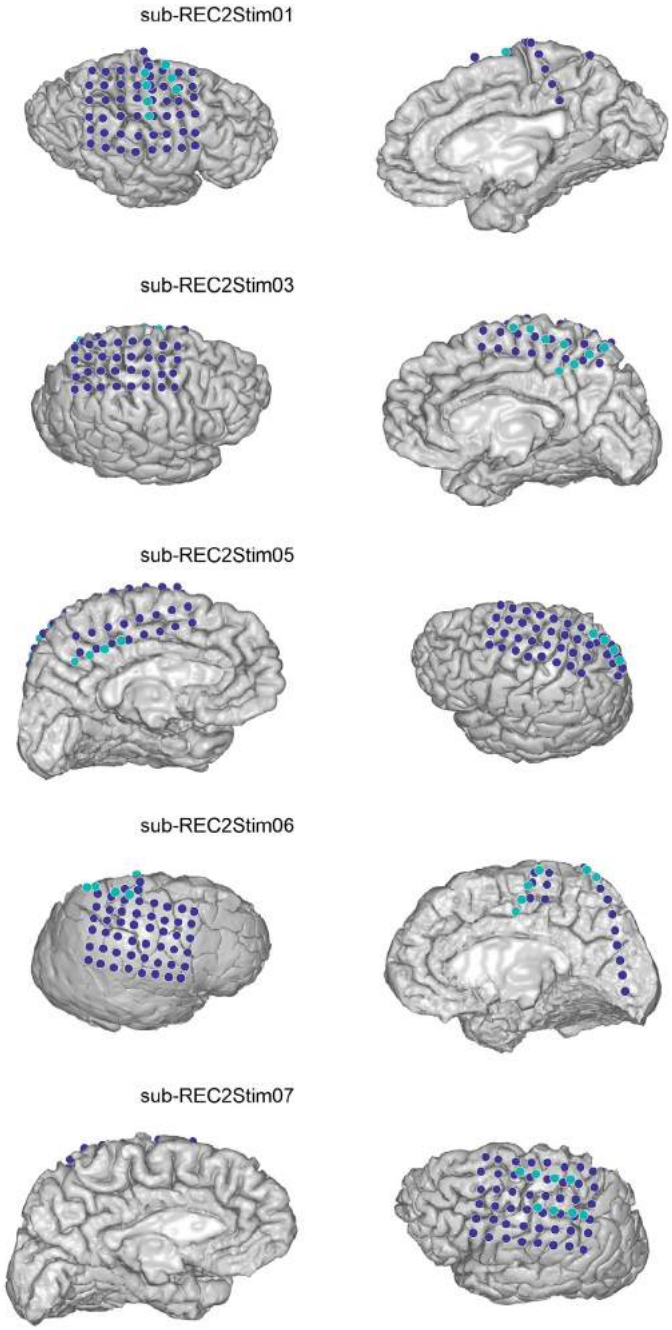
Data collection phase

Based on CT and MRI, we determined the electrode pair that covered the seizure onset zone (see Supplementary figure 6A). During the data collection phase, the subject was able to initiate the recording of seizures by pushing a button in the Patient Programmer device. With the Activa® PC+S, it is possible to record one intracranial EEG signal per electrode strip in time domain. Seizures of this electrode pair were recorded as time domain data (sample frequency of 200 Hz) (see Supplementary figure 6B). Seizures were visually annotated (DvB) in Matlab R2022b. We applied a notch filter (Butterworth, 3rd order, 47-53 Hz and 97-100 Hz) to remove 50 Hz and 100 Hz noise.

We selected epochs of 30 s pre-ictal to 30 s after ictal onset, applied a Gabor wavelet convolution and calculated the power spectrum in the frequencies 1-100 Hz in a time window of 10 s before seizure onset and the first 5 s of ictal onset (see Supplementary figure 6C). From this power spectrum, we determined two potential center frequencies for seizure detection. From this moment onwards, the subject initiates the recording of seizures with both time domain data and power domain data to see whether this power was increased during seizure onset (see Supplementary figure 6D). We calculated a linear discriminant algorithm (LDA) with a cost function for logistic regression (see Supplementary figure 6E). When this LDA exceeded 0 for a certain amount of samples (see Supplementary figure 6F), a detection was logged. In the stimulation phase, this detection would lead to a stimulation of a certain duration.



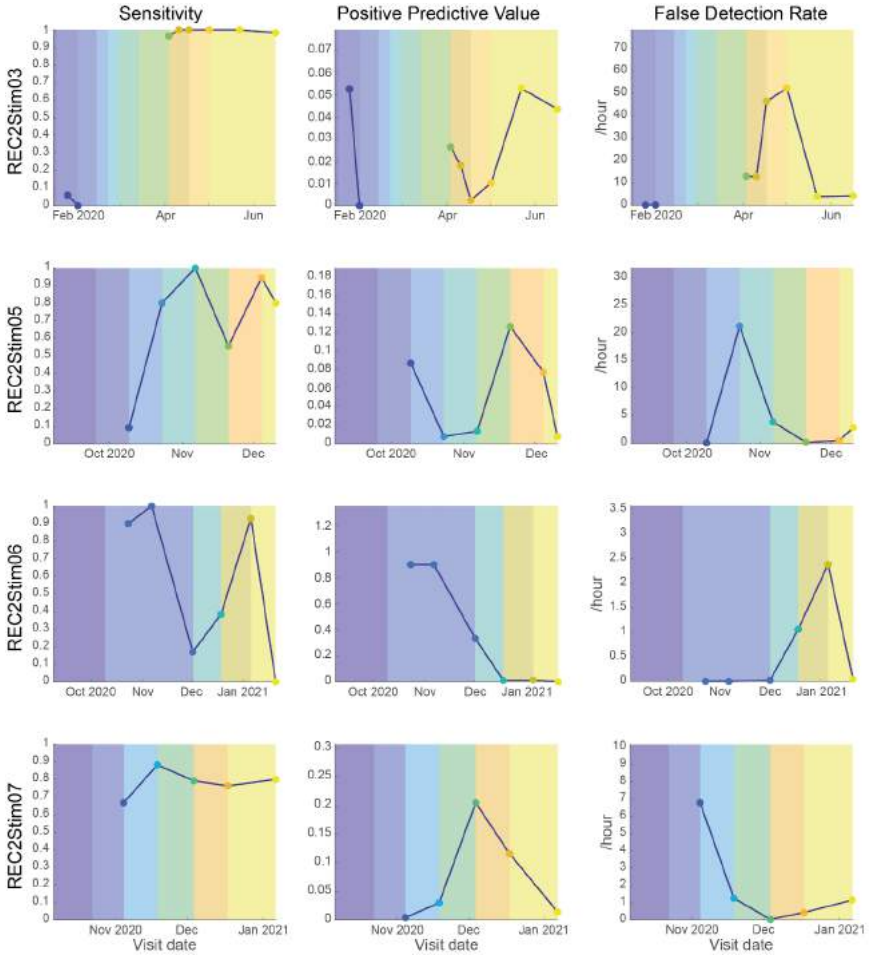
Supplementary figure 6: Detection of seizures with a linear discriminant algorithm (LDA). A) In REC2Stim03, the subdural electrode strips (light blue) were placed interhemispherically. The purple electrodes were used for seizure detection. B) One trace of time domain data of the electrodes located on the seizure onset zone (purple in A) is displayed. The vertical dotted line at 89 s indicates the start of a seizure. C) The mean power spectrum with standard error of the mean is displayed of time domain data (displayed in B) during 10 s pre-seizure onset (dark blue) and during 5 s after seizure onset (light blue). An increase in power during seizure onset is observed from 30-100Hz, with two local peaks around 40 and 60 Hz. D) Two power domain traces (X1 and X2) are displayed of the same electrode pair as the time domain trace displayed in B). The dotted vertical line at 89 s displays seizure onset. There is a clear increase in power during seizure onset in both frequency bands. E) A scatter plot is displayed with the power in 40 and 60 Hz frequency band for each sample of the power domain traces displayed in D during 10 s pre-seizure onset (dark blue, not filled) and for each sample during 5 s after seizure onset. The cost function calculated the coefficients (W1, W2, b) of the optimal discriminant with lowest costs (light grey line). F) The linear discriminant displayed in E) is used to detect seizures. The vertical dotted line at 89 s indicates seizure onset. The LDA exceeds 0 <1 s after seizure onset and a seizure is detected.



Supplementary figure 7: *For each subject with implanted neurostimulator, both the subdural grid configuration (purple) and Medtronic subdural leads (light blue) as determined with MRI and CT are displayed.*

LDA performance

During each visit in the data collection phase, recorded seizures were exported from the neurostimulator and analyzed to calculate sensitivity (true positive events/(true positive and false negative events)), positive predictive value (true positive events/(true positive and false positive events)) and false detection rate (false positive events/hour). If sensitivity was <50% or the false detection rate was >20 / hour, we improved the LDA (see Supplementary figure 8). The most effective LDA was used in the closed-loop cortical network stimulation phase.



Supplementary figure 8: Details on the performance of seizure detection during the data collection phase. Each color on the background indicates new coefficients of the LDA based on evaluation of previously recorded seizures. For REC2Stim03 eight different LDAs were evaluated before we continued to the closed-loop cortical network stimulation phase, REC2Stim06 had 4 different LDAs before we continued to the stimulation phase.

Other relevant findings – technical complications

REC2Stim03 experienced a suspected broken lead which resulted in high impedances in the electrodes used for stimulation from March 2021 onwards. Stimulation therapy through these electrodes with high impedance was not effective anymore and the patient experienced an increase in seizure frequency. We changed stimulation to an adjacent electrode pair, but seizures remain present and more optimization of stimulation parameters is needed.

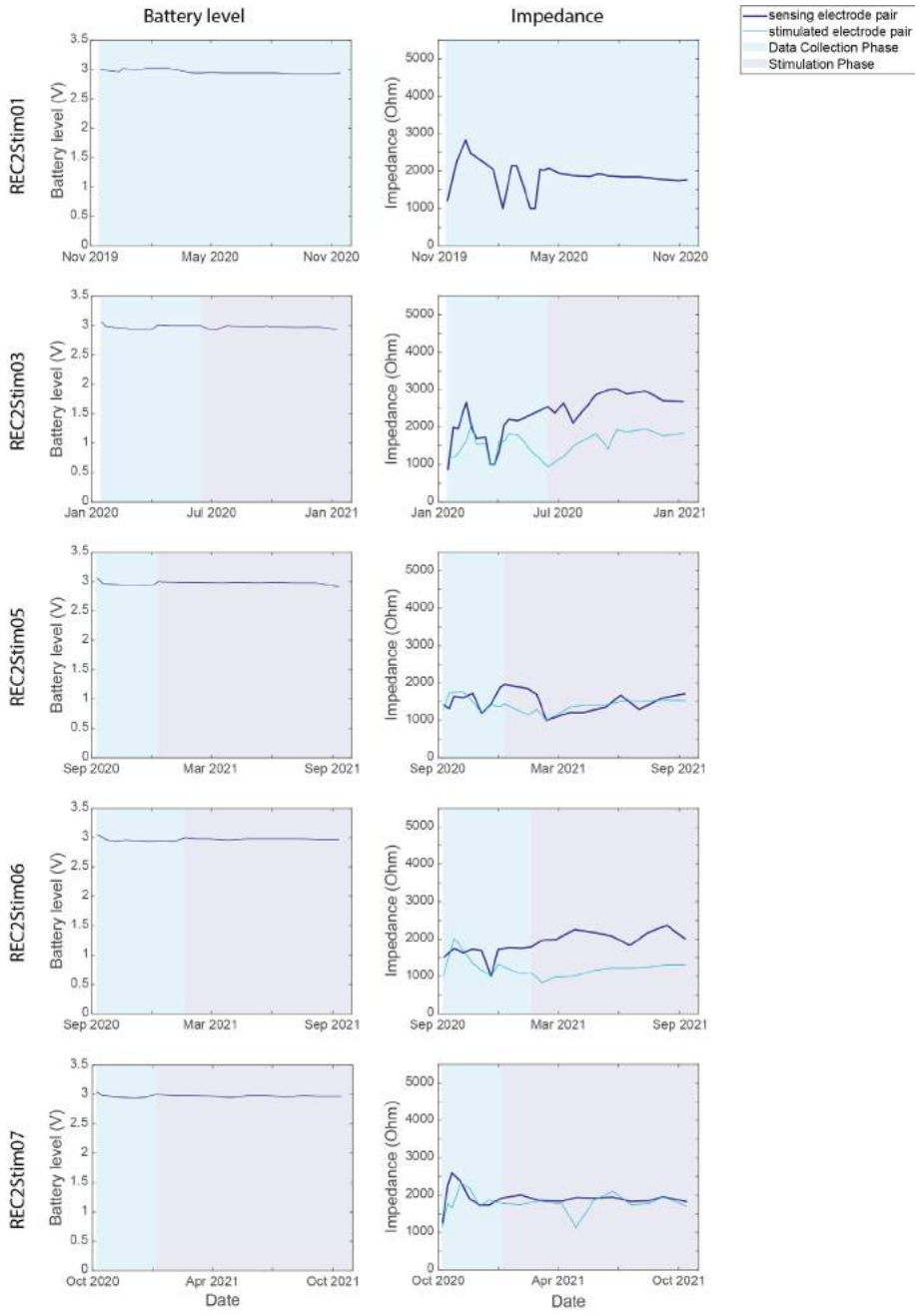
The Implantable Pulse Generator of both REC2Stim05 (June 2022) and REC2Stim07 (November 2021) had a software issue which led to continuous seizure detection which resulted in continuous stimulation. They were not able to turn off stimulation themselves. Both patients did not experience an increase in seizure frequency. During a research visit, we were able to turn off stimulation. When we turned on closed-loop stimulation again, this software issue disappeared and did not occur again.

Other relevant findings – sham stimulation

In REC2Stim03 and REC2Stim05, we initiated two weeks of sham stimulation in December 2021, because they responded well to closed-loop cortical network stimulation with seizure frequency reductions of 73%. During this period of two weeks, seizure frequency did not change. A period of two weeks might be too short to evaluate placebo effect due to an unknown duration of wash-out effect of neurostimulation [7].

Battery level and impedance

In Supplementary figure 9, the battery level and impedance of the sensing and stimulation electrode pairs are displayed. This figure indicates that closed-loop stimulation does not affect battery level significantly. We expect the battery life to have a duration of at least 4 years with similar stimulation therapy. The impedance of the sensing and stimulated electrode pairs increases in the first few months and then stabilizes.



Supplementary figure 9: Impedance and battery level of the Activa® PC+S.

PART 3: TRANSITION TOWARDS OPEN SCIENCE

A PRACTICAL WORKFLOW FOR ORGANIZING CLINICAL INTRAOPERATIVE AND LONG-TERM IEEG DATA IN BIDS

A practical workflow for organizing clinical intraoperative and long-term iEEG data in BIDS

Dorien van Blooijs*, Matteo Demuru*, Willemiek Zweiphenning*, Dora Hermes, Frans Leijten, Maeike Zijlmans on behalf of the RESPect group

* *These authors contributed equally.*
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Abstract

The neuroscience community increasingly uses the Brain Imaging Data Structure (BIDS) to organize data, extending from MRI to electrophysiology data. While automated tools and workflows are developed that help organize MRI data from the scanner to BIDS, these workflows are lacking for clinical intracranial EEG (iEEG data). We present a practical workflow on how to organize full clinical iEEG epilepsy data into BIDS. We present electrophysiological datasets recorded from twelve subjects who underwent intracranial monitoring followed by resective epilepsy surgery at the University Medical Center Utrecht, the Netherlands, and became seizure-free after surgery. These data include intraoperative electrocorticography recordings from six patients, long-term electrocorticography recordings from three patients and stereo-encephalography recordings from three patients. We describe the six steps in the pipeline that are essential to structure the data from these clinical iEEG recordings into BIDS and the challenges during this process. These proposed workflows enable centers performing clinical iEEG recordings to structure their data to improve accessibility, reusability and interoperability of clinical data.

Introduction

Today's era of big data and open science has highlighted the importance of organizing and storing data in keeping with the FAIR Data Principles of Findable, Accessible, Interoperable and Reusable Data to the neuroscientific community [197,198]. Over the past five years, a community-driven effort to develop a simple standardized method of organizing, annotating and describing neuroimaging data has resulted in the Brain Imaging Data Structure (BIDS). BIDS was originally developed for magnetic resonance imaging data (MRI[199]), but now also has extensions for magnetoencephalography (MEG [200]), electroencephalography (EEG [201]), and intracranial encephalography (iEEG [202]). BIDS prescribes rules about the organization of the data itself, with a formalized file/folder structure and naming conventions, and provides standardized templates to store associated metadata in human and machine readable, text-based, JSON and TSV file formats. Software packages analyzing neuroimaging data increasingly support data organized using the BIDS format (https://bids-apps.neuroimaging.io/apps/). However, a major challenge in the use of BIDS is to curate the data from their source format into a BIDS validated set. Several tools exist to convert MRI source data into BIDS datasets [203–207], but to our knowledge, there is currently no tool or protocol for iEEG.

The University Medical Center in Utrecht, the Netherlands, is a tertiary referral center performing around 150 epilepsy surgeries per year. The success of surgery for treating focal epilepsy depends on accurate prediction of brain tissue that needs to be removed or disconnected to yield full seizure control. People referred for epilepsy surgery undergo an extensive presurgical work-up, starting with MRI and video-EEG and, if needed, PET or ictal SPECT. This noninvasive phase is followed directly by a resection, possibly guided by intraoperative electrocorticography (EcoG), or by long-term ECoG or stereo-encephalography (SEEG) with electrodes placed on or implanted in the brain [208]. From January 2008 until December 2019, 560 of the epilepsy surgeries in our center were guided by intraoperative ECoG; 163 surgeries followed after long-term ECoG or SEEG investigation. These iEEG data offer a unique combination of high spatial and temporal resolution measurements of the living human brain and it is important to curate these data in a way such that they can be used by many people in the future to study epilepsy and typical brain dynamics.

As part of RESPect (Registry for Epilepsy Surgery Patients, ethical committee approval (18-109)), we started to retrospectively convert raw, unprocessed, clinical iEEG data of patients that underwent epilepsy surgery from January 2008 onwards, to the iEEG-BIDS format and identified six critical steps in this process. With this paper, we give a practical workflow of how we collected iEEG data in the UMC

Utrecht and converted these data to BIDS. We share our entire pipeline and provide practical examples of six patients with intraoperative ECoG, three patients with long-term ECoG and three patients with SEEG data, demonstrating how BIDS can be used for intraoperative as well as long-term recordings.

Methods and results

Patients

Patients who underwent epilepsy surgery in the UMC Utrecht from 2008 onwards are included in RESPect, the Registry for Epilepsy Surgery Patients. For patients operated between January 2008 and December 2017, the medical research ethical committee waived the need to ask for informed consent, so those patients were directly included. Since January 2018, we explicitly ask patients informed consent to collect their data for research purposes. We inform the patients that we remove identifiable information and ask specifically whether we can share the data with other researchers or commercial parties. The subjects in the dataset, shared with this paper, all gave informed consent to both sharing data with other researchers as well as sharing the data with commercial parties. We only include patients in the database when they underwent epilepsy surgery.

iEEG data

Organizing data in BIDS requires a logical grouping of study data into sessions, runs and tasks. We describe the workflow for three different types of iEEG data collected: intraoperative ECoG data collected during surgery, long-term ECoG data and long-term SEEG data collected during several days of epilepsy monitoring.

Intraoperative ECoG

Intraoperative ECoG can be performed during epilepsy and tumor surgeries to map brain function or interictal epileptiform activity. In the UMC Utrecht, intraoperative ECoG is performed in lesional epilepsy cases with concordant results of non-invasive examinations, to determine the extent of the neocortical resection, and/or the involvement of mesiotemporal structures and necessity of a hippocampectomy. It usually involves a lesionectomy and possibly a corticectomy of the surrounding tissue based on ECoG findings. It requires careful analysis of pattern, morphology, frequency and localization of interictal activity recorded directly from the exposed cortical surface, in the operating room. Over time, the clinical neurophysiologists in our center developed a standardized procedure of how to perform intraoperative ECoG recordings to tailor epilepsy surgery. Surgery with intraoperative ECoG is composed of three main situations that can be logically grouped into BIDS sessions:

- *Pre-resection sessions, consisting of all recordings (with different configurations of the grid and strips/depth electrodes) carried out before the surgeon has started the planned resection (see Figure 1A; situation 1A to 1D).*
- *Intermediate sessions, consisting of all subsequent recordings performed before any iterative extensions of the resection area (see Figure 1A; situation 2A to 2D).*
- *Post-resection sessions, consisting of all the recordings performed after the last resection (see Figure 1A; situation 3A).*

Before each situation, a photo is taken to keep track of the grid and strip/depth electrode positions (see Figure 1A). Each situation is labelled with an increasing number starting from 1 (indicative of the period in time respective to the surgical resection) and a consecutive letter starting from A (indicative of the position of the grid and strip/depth electrodes for a given session), see example in Figure 1A. Please note that there can be different rounds of intermediate recordings followed by resections if there is still epileptic activity present in the intermediate recordings. The recording after the last resection is the final post-resection session and has the highest number. This logical grouping allowed us to store the data in BIDS across sessions.

Long-term iEEG

Long-term iEEG recording is performed if results of non-invasive examinations are discordant, but one or more focal hypotheses can be formulated to explain the patient's seizure manifestations, or if the presumed epileptogenic zone is in or close to the eloquent cortex. Patients are implanted with ECoG or SEEG electrodes placed in locations that will help confirm or rule out the pre-surgical hypothesis based on the results of non-invasive examinations. After implantation of the electrodes, the patient is taken from the operating room to the invasive epilepsy monitoring unit where simultaneous video and intracranial brain signals are recorded for 5-14 days, depending on seizure frequency, type of implantation and clinical performance. During this period, seizures are recorded and functional testing and cortical mapping is performed. The goal of long-term iEEG is to define the volume of cortical tissue generating interictal epileptiform discharges, pinpoint exactly where the seizures start, and 'map' the brain tissue surrounding the presumed epileptogenic focus to identify functional tissue that may be impacted by a possible resection. If the epileptogenic focus can be localized, and a surgical strategy can be proposed, the removal of electrodes is followed by a resection. In patients implanted with ECoG electrodes, this resection often takes place in the same surgery as the electrode explantation. Patients implanted with SEEG

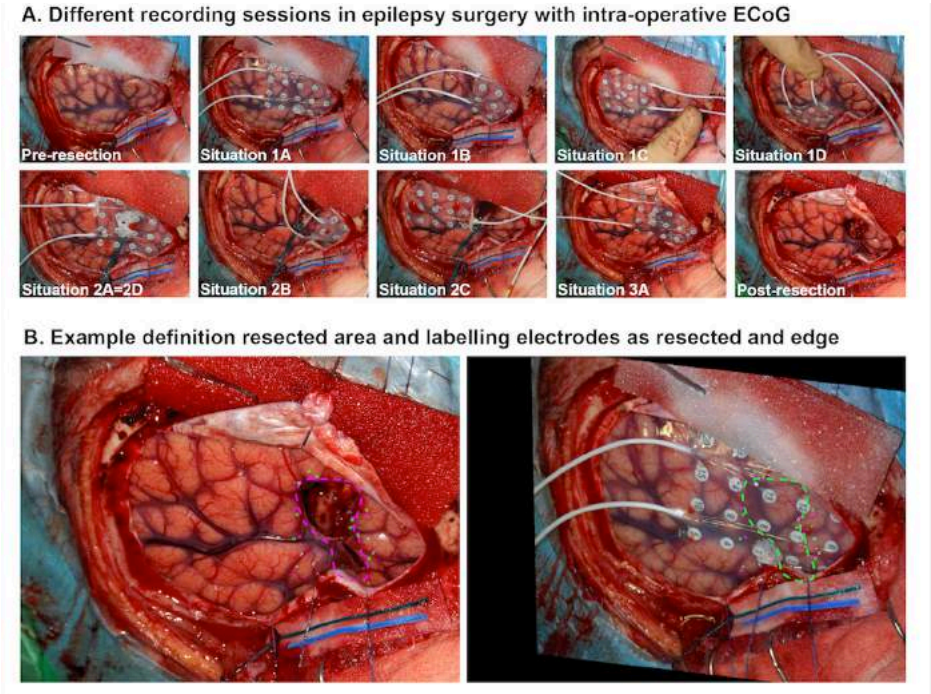

Figure 1: Patient example of the different situations composing a surgery with intraoperative ECoG (A) and how the resected and edge electrodes are defined (B). *A) Patient RESP0384 had nine situations recorded. Four situations consist of the pre-resection recordings, and are grouped under BIDS session 1A-D; four situations are recorded during intermediate periods, and are grouped under session 2A-D; there is one post-resection situation, session 3A. B) We used a custom made-software [209] to align the pre-resection and intermediate session pictures with the post-resection picture. Then we drew the resection area on the post-resection picture and this was automatically projected on the pre-resection and intermediate session pictures (green dashed line). Electrodes that were completely or partly (so exactly on the edge) on top of the resected area were defined as resected. Electrodes that were partly on top of the resected area (so exactly on the edge) or within 0.5 cm of the edge of the resection were defined as edge.*

electrodes do not need a surgery to remove the electrodes, so in these patients the resection is planned in a separate surgery.

In long-term recordings, data recorded within one monitoring period, are logically grouped in the same BIDS session and stored across runs indicating the day and time point of recording in the monitoring period.

Recording devices for iEEG

IEEG data were recorded using different Micromed headboxes (MicroMed, Mogliano - Veneto, Italy): LTM64/128 express, SD-128, Flexi. The majority of data were sampled with 512 Hz or 2048 Hz, but some patients had recordings with a sampling rate of 256

or 1024 Hz. Adtech electrodes (2008-mid 2019), PMT electrodes (since 2019) or Dixi electrodes (since mid 2018) were used.

Preparatory steps to convert to BIDS

The BIDS specification defines a folder structure for storing different types of brain imaging and electrophysiology data and was recently extended to iEEG-BIDS [202]. The folder names convey information about the subject, session, task and run and the user has to define this chain of *entities* (<key,value> pairs) to build the folder structure and name the files in an intuitive and BIDS-compatible manner.

In order to implement the iEEG-BIDS specification, different information needs to be extracted from the clinical source data. We identified six steps that were essential to organize clinical iEEG data in BIDS. These steps are: 1) assign a subject label, 2) define the session, task and run key-value pairs, 3) pseudo-anonymize the data, 4) determine the resected brain area and label electrodes as resected, edge or non-resected, 5) annotate the binary files, and 6) convert to BIDS (see Figure 2 and 3).

Data Records

We constructed two separate RESPect iEEG-BIDS databases, one for intraoperative (see Figure 2) and one for long-term (see Figure 3) iEEG recordings. Below, we describe the steps performed to organize the clinical iEEG data in BIDS in detail.

Step 1: Assign a subject label

Parallel to the conversion of the iEEG data to iEEG-BIDS, we put clinical information like patient characteristics, epilepsy type, pathology and outcome after surgery of all patients included in RESPect in Castor, an electronic data capture system [210]. We use the same convention for subject labelling in the clinical and data part: the name should start with the RESP prefix and should be followed by a 4 digits number representing the code for a patient (e.g. RESPXXXX, where XXXX is a 4 digits number).

An overview of patients included in the RESPECT_acute_iEEG-BIDS database and in the RESPECT_longterm_iEEG-BIDS database is given in participants.tsv. This file contains the RESP-number, the number of sessions, sex and the age of the patient when the data was recorded.

Step 2: Define the session, task and run key-value pairs

The definition of the session, task and run differs between the two types of iEEG recordings and will be explained in the following subsections.

Intraoperative ECoG

We decided that each recording situation as explained in the iEEG data section, represents a *session* of the BIDS specification. We assigned the situation name to the key-value pair related to the *session* (e.g. ses-SITUATION1A). We did this, because the location of the electrodes changes with each recording situation, and are assigned at the session-level.

The intraoperative recordings we are currently converting to the BIDS format, are ongoing recordings during anesthesia without any stimulus (i.e. "resting state"). We decided to assign the label "acute" to the key-value pair related to the *task* (e.g. task-acute). Recordings where intraoperative somatosensory evoked potential (SSEP) is performed, or recordings where the patient is woken up to perform language or motor testing are defined as *task*-SSEP and *task*-stimulation.

We did not define the optional *run* key-value pair for intraoperative recordings, since only one run was recorded of each task. Once the session and task have been defined, it is possible to create the folder structure and name the files (Figure 2D).

Long-term iEEG

iEEG-files that were recorded within one monitoring period were categorized in the same *session*. When extra electrodes were added/removed during this period, the *session* was divided into ses-1a and ses-1b. Some patients had two long-term iEEG periods with, for example, first ECoG and second SEEG electrodes. These patients have a ses-1 and a ses-2. We use the optional *run* key-value pair to specify the day and the start time of the recording (e.g. run-021315 means day 2 after implantation (which is day 1 of the monitoring period), at 13:15). We use the consecutive days after the implantation in the run key-value pair, because the timing of a specific task relative to the surgery and optional medication withdrawal might be important when investigating iEEG signals. With the consecutive days after surgery in the run key-value pair, it might be easier to include/exclude specific recordings to minimise the effect of certain events on the research question you would like to investigate. Using the run key-value pair with such coding strategy is specific for our laboratory and it was implemented to simplify the selection of the files without the need to parse other metadata.

The *task* key-value pair in long-term iEEG recordings describes the patient's state during the recording of this file. Different tasks have been defined, such as "rest" when a patient is awake but not doing a specific task, "sleep" when a patient is sleeping during the majority of the file, or "SPESclin" when the clinical SPES (Single Pulse Electrical Stimulation) protocol was performed in this file [89]. Other task definitions can be found in the annotation syntax (see step 5). Once the session, run and task have been defined, it is possible to create the folder structure and name the files (Figure 3D).

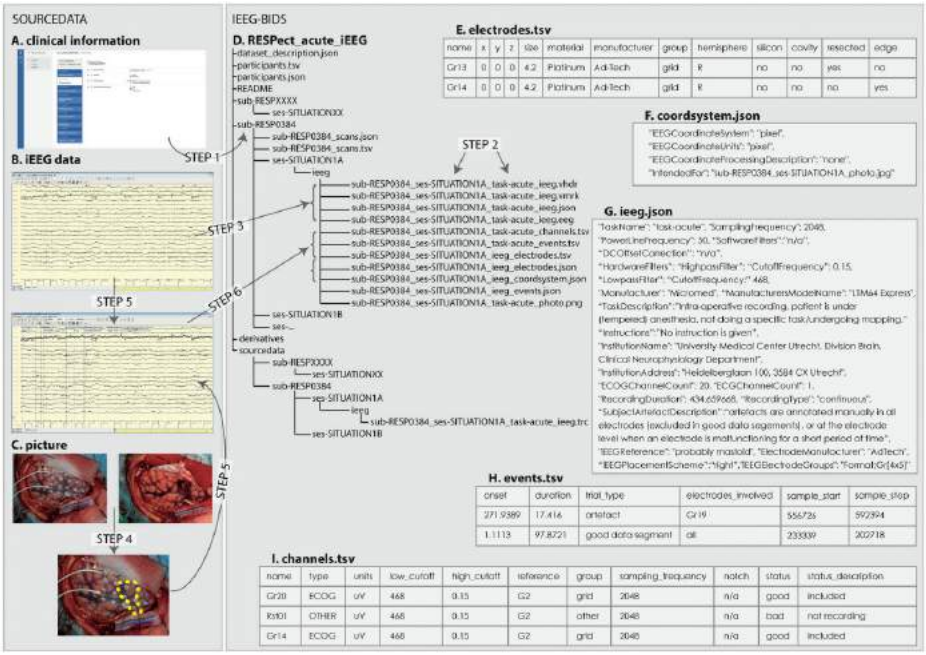

Figure 2: Overview of the steps required to convert the intraoperative ECoG recordings to iEEG-BIDS. In the left box, the sourcedata is displayed with A) the clinical information in an electronic data capture system, B) the raw (upper subplot) and annotated (lower subplot) acute ieeg recording in the clinical eeg system, C) the pictures showing the electrode positions: one pre-resection (left) and one post-resection (right), which are combined in a figure (below) with the resection indicated on top of the electrode grid with a dotted green line. In the right box, in D) the iEEG-BIDS data structure is displayed and in E-I) examples of BIDS specific files that should be present inside each sub-folder. The specific steps in this figure are explained in the text. All subplot results from subject RESP0384.

Step 3: Pseudo-anonymize data

Intracranial EEG data are collected in (proprietary) binary formats that may include protected subject information. The binary format used in our center is by Micromed (TRC-file). We pseudo-anonymized the TRC-files, because a BIDS data viewer is still missing and we wanted to allow our clinicians and researchers to visualize the pseudo-anonymized and annotated data easily. We manually changed the patient names to RESPect identification numbers, the date of birth to 1-1-year in the Micromed patient identifier, and removed the patient names from recording montages. We subsequently ran Matlab code to further pseudo-anonymize all fields in the rest of the TRC-file (see https://github.com/UMCU-EpiLAB/umcuEpi_acute_ieeg_respect_bids/anonymization and https://github.com/UMCU-EpiLAB/umcuEpi_longterm_ieeg_respect_bids/anonymization for the code implementation). Pseudo-anonymization

means that there exists a table with the association RESPect identification number and identification number used to store the patient in the hospital database system. This table is accessible only to a restricted number of people: physicians involved in the study and BIDS database administrators.

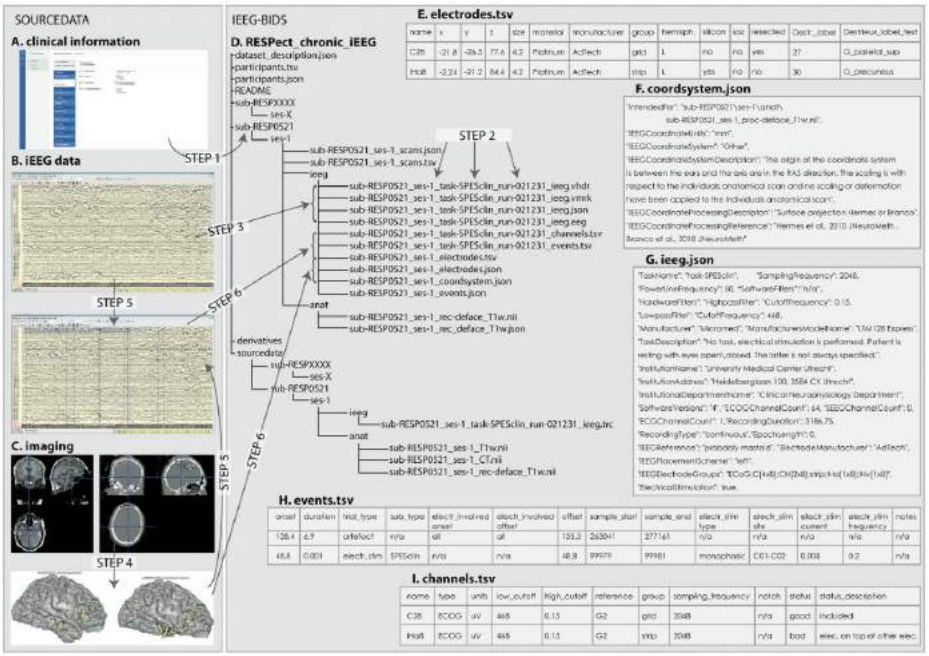

Figure 3: Overview of the steps and sourcedata required to convert the long-term iEEG recordings to iEEG-BIDS. In the left box, the sourcedata is displayed with A) the clinical information in an electronic data capture system, B) the raw (upper subplot) and annotated (lower subplot) long-term ieeg recording in the clinical eeg system, C) the defaced MRI (left) and co-registered CT (right), resulting in two patient specific brain renderings with the electrodes in yellow: one pre-resection and one post-resection. In the right box, in D) the iEEG-BIDS data structure is displayed and in E-I) examples of BIDS specific files that should be present inside each sub-folder. The specific steps in this figure are explained in the text. All subplots result from subject RESP0521, except subplot C which illustrates the imaging processes in SEEG subject RESP0749.

Step 4: Determine the resected brain area and label electrodes as resected, edge or non-resected

In both intraoperative and long-term iEEG recordings we added "resected", "edge" and "cavity" labels to our electrodes.tsv, but the method used to do so differs (see description below).

Intraoperative ECoG

In intraoperative ECoG, we defined the "resected", "edge" and "cavity" electrodes using the pictures taken in the operating room. We used a custom made-software [209] to align the pre-resection and intermediate session pictures with the picture representing the end of the surgery. Then, we drew the resection area on the post-resection picture and this was automatically projected on the pre-resection and intermediate session pictures (see Figure 1B and 2C; green/yellow dashed line). Electrodes that were completely or partly (so exactly on the edge) on top of the resected area were defined as resected. Electrodes that were partly on top of the resected area (so exactly on the edge) or within 0.5 cm of the edge of the resection were defined as edge. Electrodes that were above a resection cavity from an earlier surgery or a previous situation in the current surgery (so not recording brain signals) were defined as cavity.

Long-term iEEG

In long-term iEEG, we co-registered the pre-operative MRI to the CT with electrodes, and the post-operative MRI to the co-registered pre-operative MRI. We subsequently superimposed the CT with electrodes onto the co-registered post-operative MRI (see https://github.com/UMCU-EpiLAB/umcuEpi_longterm_ieeg_respect_bids/electrode_positions/scripts/elecPos03_process_postOperativeMRI.m) and defined electrodes as "resected", "edge" and "cavity" using the same definitions as above.

Step 5: Annotate the binary files with custom syntax

In order to implement the BIDS specification, different metadata information is necessary; for example: artefacts, good segments of the data, period of sleep, stimulation paradigms (like Single Pulse Electrical Stimulation (SPES) or somatosensory evoked potentials (SSEP)). We therefore decided to annotate our TRC-files with a custom syntax, using the proprietary Micromed visualization software (SystemPlus v. 1.04.0197) to include the metadata (Figure 2B and 3B). The syntax and scripts used to enrich the original TRC-files and automatically create the BIDS files are available at https://github.com/UMCU-EpiLAB/umcuEpi_acute_ieeg_respect_bids/ for intraoperative and at https://github.com/UMCU-EpiLAB/umcuEpi_longterm_ieeg_respect_bids/ for long-term ECoG and SEEG recordings.

Step 6A: Convert to BIDS – Electrodes and coordinates

In the electrodes.tsv, the position, size and other properties of the iEEG contacts are stored (Figure 2E and 3E). The coordsystem.json file was intended for specification of the method and reference system used to determine the electrode positions (Figure

2F and 3F). The definition of the electrode positions differs between the intraoperative and long-term iEEG recordings and will be explained in the following subsections.

Intraoperative ECoG

Electrode coordinates during intra-operative recordings can be localized on 2D pictures taken during surgery. However, electrodes recording from the same brain tissue (i.e. overlapping parts from Situation 1A and 1B) would have different x,y coordinates based on different pictures taken during Situation 1A and 1B. The goal of these recordings is to identify epileptic versus normal tissue, and relate that to outcome. Therefore, we set the x, y, z coordinates in the electrodes.tsv file of the intraoperative iEEG data to zero, even though the iEEG-BIDS specification allows them to be given in 2D space from operative photos. Given a picture for a situation, it is possible to have the relative location between the electrodes (i.e. the electrode names and channel names have a correspondence with the picture: Gr11 is contact point 11 in the picture. See example sub-RESP0059_ses-SITUATION1A_photo.jpg). In the coordsystem.json file, we included the name to the picture taken before starting the recording (Figure 2C).

Long-term iEEG

The electrodes.tsv of long-term iEEG recordings contains the patient-specific MRI x, y, z coordinates, size and other properties of the electrodes. The CT was co-registered with the defaced T1 weighted pre-operative MRI. The MRI was segmented using Freesurfer software. The electrodes were localized on the CT-scan, corrected for brain shift and placed on the cortical surface (Figure 3C). The code (https://github.com/UMCU-EpiLAB/umcuEpi_longterm_ieeg_respect_bids/electrode_positions) to do this, was adapted from Hermes et al. [137] and Branco et al. [211]. In the coordsystem.json, the method and reference system used to determine the electrode positions is described. We additionally assigned electrodes to regions of the Destrieux [138] and DKT atlases[212] extracted using Freesurfer [213].

Step 6B: Convert to BIDS – Information about the recording and channels used

The _ieeg.json file contains metadata about the recordings (Figure 2G and 3G). In the field *iEEGElectrodeGroups,* we defined a way to express the used recording scheme. Specifically, we extracted the annotation we made in the TRC-file using the following syntax (see Step 5):

Format; followed by the electrode name and dimensions of the grid and/or strip/depth electrodes used.

In the example in Figure 2G, "Format;Gr[4x5]" implies that a rectangular grid with 20 electrodes was used for the intraoperative ECoG recording. In the example in Figure 3G, "ECoG;C[4x8];CH[2x8];strip;IHa[1x8];IHv[1x8]" implies that two grids and two strips were used for the long-term ECoG recording. The electrode names typ8ically are related to the anatomical area they are targeting (i.e. IH for interhemispheric anterior and posterior, C for central). A large electrode grid could cover other anatomical areas than the target area. It is recommended not to rely on the electrode names but better use the mapping of the contacts to an anatomical region defined by one of the atlases.

The channels.tsv file is intended for storing information related to the channels in a recording, such as the recording montage, sample frequency, units etc. (Figure 2I and 3I). The variables *status* and *status description* specify if the channels are available for usage and give a reason if a channel is not available. We used the annotations made in the TRC-file in step 5 to extract which channels contain good or bad signal, and defined the different reasons for bad signal in status description, for example:

1. *Noisy - after visual inspection, a reviewer declared the channel as bad because the signal is noisy. These channels are annotated as "Bad;..." in step 5 (Figure 2B and 3B). The BIDS conversion will put their BIDS status to 'bad', with 'noisy after visual inspection' as BIDS status description.*
2. *Silicon - the electrode was placed on top of the silicon of another grid or strip; few brain signal is recorded. These channels are annotated as "Silicon;...". The BIDS conversion will put their BIDS status to 'bad', with 'electrode on top of other electrode' as BIDS status description.*
3. *Screw - this annotation was only present in SEEG recordings. It defines an electrode that was not recording cortical signals, but located in the screw outside the brain. This was determined from the electrodes extracted from the CT and co-registered on the pre-operative MRI. These channels were annotated as "Screw;...". The BIDS conversion will put their BIDS status to 'bad', with 'located in screw' as BIDS status description.*

Step 6C: Convert to BIDS – Events in the recording

The events.tsv file contains a table with the onset, duration, and channels involved in events present in a recording. We annotated the onset and offset of events in the TRC-files with a specific syntax in step 5. These annotations were converted to onset and duration in the events.tsv files. The events differed between intraoperative and long-term iEEG recordings and were explained in more detail in the sub-RESPXXXX_ses-X_events.json file in the subject's directory of the respective iEEG-BIDS database.

Intraoperative ECoG

In intraoperative ECoG, we used *event* definitions to mark good, clean data segments without artefacts due to equipment in the operating room or due to surgical manipulation, and without burst-suppression as a result of remnants of propofol anesthesia. If intra-operative SSEP was performed or if the patient was woken up to perform language or motor testing, additional *event* annotations were added in a column defined in an accompanying _events.json.

Long-term iEEG

In long-term iEEG, task definitions and event annotations are often coupled: if a task (for example sleep) was defined and annotated at the beginning of the file in step 5, a period of sleep was annotated in the file with SI_on and SI_off. This period of sleep was stored in the events.tsv as an event with onset (e.g. time corresponding to SI_on marker) and duration (time between SI_on and SI_off markers). Artefacts, seizures, stimulation, motor tasks etc. are also annotated and added in the events.tsv.

The optional scans.tsv file contains an overview of all files present in a session of a patient, and the type of tasks and events present in these files. This is useful to decide which recordings can be used to answer a specific research question.

Step 6D: Convert to BIDS - TRC to supported file format

TRC-files are not part of the set of supported binary file formats of the BIDS specification. We therefore converted our iEEG data to BrainVision Core Data Format (.vhdr,.eeg,.vmrk).

Step 6E: Convert to BIDS – Structure sourcedata

The pseudo-anonymized and annotated TRC-files of each patient were stored in their subfolder in the sourcedata folder. For intraoperative iEEG, this folder also contains the original pictures of the electrode positions taken in the operating room (before aligning them with the post-resection image and drawing the resection cavity). For long-term iEEG, this folder also contains CT scans with electrode positions and raw T1 weighted MRI scans. The defaced MRI is located in the anat-subfolder in each specific patient folder. The derivatives-folder contains a freesurfer folder with each subject's MRI scans processed with freesurfer.

Final Remarks

Clinical intracranial EEG data recorded to guide epilepsy surgeries consists of heterogeneous data that is highly dependent on the center and the approach to

epilepsy surgery. We proposed a practical guideline on how to organize full clinical iEEG epilepsy data through the BIDS specification. These data include intraopreative electrocorticography recordings, long-term electrocorticography recordings and stereo-encephalography recordings. We described the six steps of the pipeline that are essential to summarize and structure the rich data and metadata in a homogeneous and systematic way. We outlined the minimal and essential information required for a downstream analysis on intracranial recordings. This represents our main clinical research goal in the UMCU: improving epilepsy surgery. Several other clinical research questions that could be investigated through the dataset are about the relationship between iEEG and the type of pathology, side of surgery, MRI abnormalities and functional outcome, like cognition. Furthermore, structuring data into BIDS benefits other research fields interested in for example brain function in physiological/pathological resting-state brain networks. To shape our data structure, we defined some custom terminology which is characteristic for our center (i.e. the term "Situation" to describe a certain phase of the epilepsy surgery). This terminology is open to discussion aiming to make data more transparent, reusable and reproducible.

With this practical workflow, we hope to enable centers performing clinical iEEG recordings to structure their clinical data and we hope to further stimulate the discussion on the standardization of clinical iEEG data for research purposes.

Information Sharing Statement

The data of six intraoperative, and a sleep recording, a recording containing a seizure and (if available) a recording containing a stimulation session of three long-term ECoG and three long-term SEEG patients was converted to the iEEG-BIDS format as described above and are stored in openneuro.org with the following doi: https://openneuro.org/datasets/ds003844/versions/1.0.3, https://openneuro.org/datasets/ds003848/versions/1.0.3. Our effort aimed at providing a systematic structure which is as general as possible to enable inclusion of other events or tasks in the future. It is up to the researcher to select proper data segments from the data in order to answer a specific research question (that can be stored in a derivative or in a new BIDS dataset). We provided a starting point that is structured and homogeneous compared to the raw data which is most of the time custom to the specific patient. The dataset we share, is one of the few examples with three different iEEG techniques.

Technical Validation

We ran our example patients through the BIDS Validator App [214], which could be found at the following address: https://bids-standard.github.io/bids-validator.

The long-term ECoG and SEEG examples passed the validation procedure. The intraoperative ECoG examples passed the validation procedure with zero's as electrode coordinates in the electrodes.tsv (details step 6a). The datasets are therefore compatible with the official iEEG-BIDS release.

Code Availability

We provided two different sets of codes because we have two different input data (intraoperative and long-term) based on different protocols and strategies of acquisition. The code has to be used according to the type of data (intraoperative or long-term): https://github.com/UMCU-EpiLAB/umcuEpi_acute_ieeg_respect_bids/ for intraoperative ECoG and https://github.com/UMCU-EpiLAB/umcuEpi_longterm_ieeg_respect_bids/ for long-term iEEG.

SUMMARY AND GENERAL DISCUSSION

SUMMARY

Summary

Patients with epilepsy arising from the primary sensorimotor cortex have disabling seizures that are hard to treat with the standard treatment options e.g. anti-seizure medication and epilepsy surgery. The region where these seizures are generated, can be well localized due to the semiology involved with seizure onset. However, epilepsy surgery rarely leads to seizure freedom, because resections are incomplete to avoid functional deficits post-surgery. The fact that the seizure onset zone (SOZ) can be well localized facilitates targeted electrical neurostimulation, but direct electrical stimulation in this area might also affect motor performance.

The aim of this thesis was to lay a foundation for a new treatment option with cortical network closed-loop electrical stimulation for patients with epilepsy arising from the primary sensorimotor cortex.

Part 1: characteristics of effective connectivity in brain networks

A first step before clinical use of closed-loop electrical stimulation in a cortical network is to have more insight in these cortical networks in the human brain. One method to investigate effective connectivity in brain networks is by applying Single Pulse Electrical Stimulation (SPES) to two adjacent electrodes and evaluation of the cortico-cortical evoked potentials (CCEP) evoked by those stimuli in other electrodes on the subdural electrode grid. Previous studies have shown that there is a network connection between the stimulus pair and the response electrode, but little is known about these networks in different conditions and whether these networks are suitable for selecting a stimulation site for closed-loop cortical network electrical stimulation therapy. Chapter 2 explores the differences in the effective connectivity characteristics in and outside epileptogenic tissue. We analyzed the indegree, outdegree, betweenness centrality, percentage of bidirectional, receiving and activating connections and the percentage of connections toward (non-)epileptogenic tissue. Electrodes in epileptogenic tissue showed higher values for in- and outdegree. We did not find a difference for betweenness centrality. We also found more bidirectional and fewer receiving connections in the epileptogenic tissue. The epileptogenic tissue appeared densely connected with itself, with only little input from non-epileptogenic regions. On the one hand, these general results offer options for delineation of the epileptogenic region, since the network is organized in a different way in the epileptogenic tissue. On the other hand, this opens prospects for electrical stimulation therapy, since connections towards epileptogenic tissue can be revealed and targeted.

The results in Chapter 2 are obtained when applying SPES in the awake patient during clinical evaluation for epilepsy surgery, but it is unknown how cortical networks change during epilepsy surgery under anesthetics. This information is relevant when we would want to define the stimulation site in the operating room, when the neurostimulator is implanted. In Chapter 3, the effect of anesthetics on effective connectivity is investigated. In six patients, SPES is applied while the patient is awake, and while under anesthetics during the surgery where the subdural electrode grids are explanted. We found that the network topology remained similar in both situations: stimulus pairs with a high outdegree in the awake state, evoked less CCEPs under anesthetics but still had a high outdegree compared to other stimulus pairs under anesthetics. Response electrodes with a high indegree in the awake state still had a relatively high indegree under anesthetics, although the absolute number of evoked CCEPs was decreased.

In Chapter 4, we applied SPES in 74 patients aged 4-51 years old. From the evoked CCEPs, we calculated transmission speed across and within brain lobes by dividing the latency by the length of the underlying white matter tracts. We found that the transmission speed increases with age. This is very important information when we would use accurate computational models of brain networks to determine a potential stimulation site and predict what stimulus parameters would be most effective in the individual patient. We also found that the number of connections was not affected by age, suggesting that we could reveal connections towards the epileptogenic tissue in patients with different ages. This fundamental research lays the foundation to further investigate properties of promising stimulation sites for cortical network electrical stimulation.

Part 2: neurostimulation as treatment for epilepsy patients

In part 2, we explored therapeutic neurostimulation for patients with epilepsy. Chapter 5 reviewed all studies between 1990-2017 with cortical electrical stimulation to a neocortical seizure focus with an implanted device. Either open-loop (in total 21 patients were included) or closed-loop stimulation (in total 256 patients) was applied. With open-loop stimulation, electrical stimuli are applied in a continuous or cyclic way (e.g. 1 minute on, 5 minutes off). With closed-loop stimulation, electrical stimuli are only applied when certain events are detected (e.g. seizure onset, interictal spike patterns). Patients receiving open-loop stimulation experienced impressive (72-100%) reductions in seizure frequency. Patients receiving closed-loop stimulation experienced a seizure frequency reduction of 44% for year 1, which increased to 53% for year 2. Although the results in the open-

loop stimulation studies are promising, there might be a publication bias since only 21 patients received this type of stimulation. Chapter 6 investigates whether we could use temporary effects of SPES on interictal activity as a surrogate marker for long-term neuromodulation treatment. We found that when a stimulus site was connected to the epileptogenic region, more neuromodulation, by means of larger change in number of interictal discharges, or decrease in broadband power, was observed. This indicates that SPES could be used to determine a potential stimulus site with effect in the epileptogenic region.

With the knowledge we obtained in the previous chapters, we were able to initiate an early feasibility study in Chapter 7 in which we applied closed-loop cortical network electrical stimulation in five participants with epilepsy arising from the primary sensorimotor cortex. During an intracranial grid monitoring period, it was concluded that the epileptogenic region was located in eloquent motor cortex and that epilepsy surgery was not possible without inducing functional deficits. We determined a stimulation site outside the primary sensorimotor cortex with a connection to the epileptogenic region. We implanted one subdural lead covering the stimulation site, and one lead covering the epileptogenic region. We collected electrocorticographic data of seizures and improved a linear discriminant algorithm to detect the seizures of each patient. We then applied electrical stimulation upon seizure detection. One year after implantation of the neurostimulator, the mean seizure frequency was decreased by 54% (range 26-77%), without affecting motor performance. This study provides a proof of concept that closed-loop cortical network stimulation reduces seizure frequency without affecting motor performance. In the coming years, we will keep finetuning stimulus parameters in order to reduce seizure frequency even further.

Part 3: transition towards open science

In the past decade, open science has become more and more important. This is reflected in the FAIR principles, which means that data should be findable, accessible, interoperable and re-usable. When more data is available according to these principles, this could enhance progression in medical inventions which might benefit patients. One data structure that is often used in neuroscience is the Brain Imaging Data Structure (BIDS). A lot of pre-processing is needed in order to structure data in a way that can be easily used by a large group of members of the neuroscience community. In Chapter 8, we described a practical workflow how to organize clinical intraoperative and long-term intracranial EEG data into this BIDS structure. We also shared practical examples of twelve patients to demonstrate how intracranial EEG recordings can be converted to BIDS. To further participate in the

open science movement, we made data available on openneuro.org of research executed in Chapters 3, 4 and 6.

In conclusion, we laid a foundation for cortical network closed-loop electrical stimulation in this thesis. First of all, we applied SPES and investigated the effective connectivity of brain networks evoked by SPES. We found that the cortical network is organized differently in the epileptogenic region, and that this network within and across several lobes becomes faster with age. Furthermore, we found that this network is marginally altered under anesthetics: we found less connections, but important nodes remained relatively important under anesthetics. This gives us opportunities to determine the effective connectivity in brain networks during surgery. We also used SPES to investigate transient effects of stimulation on interictal activity and found that these neuromodulatory effects occurred more often when there was a connection between the stimulus site and the electrode on epileptic tissue. This gave us starting points to determine promising stimulation sites for neurostimulation therapy. All research finally led to the initiation of an early feasibility study in which we applied cortical network stimulation in order to reduce seizure frequency in patients with epilepsy arising from the primary sensorimotor cortex. A mean seizure frequency reduction of 54% (range: 26-77%) was obtained across patients, showing that this therapy is promising, but also needs optimization to further decrease seizure frequency.

GENERAL DISCUSSION

General discussion

We aimed to investigate an alternative treatment for patients with epilepsy arising from the primary sensorimotor cortex. Seizures in this group of patients are often difficult to treat with anti-seizure medication and epilepsy surgery rarely leads to seizure freedom because of resection limitations to avoid functional deficits.

We investigated cortical networks, reconstructed from electrical perturbation in one electrode pair, evoking cortico-cortical evoked potentials (CCEPs) in other electrodes. We used this patient-specific cortical network to determine a stimulation site for therapeutic neurostimulation. This discussion provides a synthesis of wat we learned, and what challenges are waiting.

Characteristics of effective connectivity in brain networks

Single Pulse Electrical Stimulation (SPES) was first used to map connectivity of language [44] and motor cortices [43], and was then extended to evaluate connections in the frontal-temporal lobe [45], the parietal-frontal lobe [90], the limbic network [215], and other brain structures [144]. In the past decade, SPES has been gaining interest as a tool to probe pathological regions in epilepsy [47,54,60,216–218] and to localize epileptic networks [50,71,219,220], as well as to investigate cortical excitability, by means of the CCEP amplitude [51,52,221,222].

We found that networks in the epileptogenic region were denser than in non-epileptogenic tissue and that the epileptogenic region has only a few incoming connections (**Chapter 2**). This is essential information when these connections are used to find a target for electrical stimulation therapy: it is possible that the options for cortical network stimulation therapy are limited. However, in all patients, we found a connection towards the epileptogenic tissue, so it could be possible to find a target outside epileptogenic tissue to apply cortical network stimulation therapy.

We presume that if SPES would be used to determine a stimulation site for therapeutic neurostimulation, SPES would be applied while the patient is under anesthetics for implantation of the neurostimulator. However, an important caveat is the effect of brain state, like sleep [223] or anesthetics [224,225], on the evoked responses to SPES stimulation and therefore, the effective connectivity. We found less connections when the patient was under anesthesia (**Chapter 3**). This suggests that when using SPES during surgery to target a stimulation site for electrical stimulation therapy, a number of potential stimulation sites might be missed. On the other hand, the remaining connections might be stronger and therefore a better target for therapeutic neurostimulation, since nodes

that were important in the awake state, with high indegree, outdegree or betweenness centrality, remained important under anesthesia.

In more recent years, SPES has been used [226,227] to investigate the effect of variations in stimulus parameters to evoked potentials. One study [227] found that current intensity and pulse width influence latency, amplitude and waveform of the CCEPs. When the researchers [227] analyzed the amplitude of the stimulus artifact as a measure of the strength of activation of surrounding tissue during stimulation, they found that the amplitude of this stimulus artefact increased with charge, but more specifically with pulse width, indicating that pulse width may affect spatial selectivity of the stimulation more than current intensity does. Shorter pulse width stimulations might produce more spatially selective activation in applications such as deep brain stimulation, or cortical stimulation therapy. Those studies mainly analyze the CCEP amplitude, stimulus artefact and spatial distribution. Analysis of changes in N1 latency is still lacking, but this might give additional information about the effect of various stimulus parameter sets on the response of brain tissue. In Chapter 4, we found that the N1 latency decreases with age. It is important to take this into account when interpreting N1 latencies across subjects as a measure to investigate the effect of different stimulus parameter sets to evoked potentials.

N1 latencies and transmission speed play a key role in the dynamics of the brain [123]. Human studies only investigated indirect transmission speed by means of morphology of white matter fibers or measurements with Diffusion Tensor Imaging [123]. Chapter 4 gives a unique insight in how transmission speed changes with age by directly measuring the evoked potential in a response electrode after probing another electrode pair. This information is very important when modeling long-range propagation of cortical activity [228], in which regional heterogeneity in excitatory and inhibitory synaptic properties account for the wide repertoire of brain dynamics [229]. Accurate models could enhance prediction of optimal stimulation parameters and site for electrical stimulation therapy.

Responses to SPES as an indication of effective neurostimulation therapy is limited. It is possible that repeated pulses, like paired-pulse stimulation, or higher frequency stimulation in trains, act to engage larger networks while the mechanisms underlying responses to SPES might not engage these widespread networks. Further tests may be needed to interpret the differences between low frequency evoked responses such as CCEPs, and responses to high frequency stimulation [226] and to correlate these responses with clinical outcome e.g. seizure frequency and severity.

The optimal stimulation site

In spite of many years of applying electrical stimulation therapies for epilepsy, like deep brain stimulation (DBS), vagal nerve stimulation (VNS) and cortical stimulation (CS), we do not yet fully understand what makes these treatments effective or ineffective [230,231], and how to predict in which patients DBS, VNS or CS might be successful. Since these treatments are considered palliative and rarely lead to seizure-freedom, it remains open whether further optimization might lead to better seizure control [230]. Biomarkers which predict optimal sites for electrical stimulation therapy might help to determine what type of therapy is most promising in the individual epilepsy patient.

In **Chapter 6**, we suggested that the neuromodulatory effects of SPES on interictal epileptiform activity could be such a potential biomarker for finding an optimal stimulation site. In **Chapter 7**, we used the hypothesis from Chapter 6 to apply neurostimulation therapy in an early feasibility study. Unique in this study is that we applied neurostimulation therapy in healthy tissue, connected to the epileptogenic region. In this study, we implanted one subdural strip on a location that was connected to the epileptogenic tissue and showed power suppression in the epileptogenic tissue when SPES was applied. In all patients who achieved closed-loop cortical network stimulation therapy, seizure frequency was reduced with on average 54% (range: 26-77%). This effect is similar to seizure frequency reduction after 2 years of closed-loop stimulation in the Neuropace trial [165]. This suggests that closed-loop cortical network stimulation therapy is a promising alternative to other electrical stimulation therapies.

We did not apply cortical stimulation therapy in other regions, like the epileptogenic region, or a region that did not show these neuromodulatory effects, as described in Chapter 6. Therefore, we cannot compare long-term treatment across different stimulation sites and make conclusions on the most effective site for stimulation. Scheid et al. [232] found that suppressing seizures required less energy when stimulation was applied in the seizure onset zone (SOZ). However, they also mention that it is likely that multiple cortical locations may be targeted to modulate the epileptogenic network.

Other studies with intracranial EEG [188,233,234] have shown that functional connectivity is altered in responders to CS. These studies, including the studies in this thesis, might suggest that it is mandatory to first undergo an intracranial EEG recording to find the optimal location for electrical stimulation therapy. This is unfavorable since such monitoring is very costly and poses a high burden for the patient. It is, therefore, important to find non-invasive biomarkers from neuroimaging or EEG, that could predict optimal neurostimulation therapy.

A recent study with fMRI [187] shows that non-responders and responders to DBS can be distinguished, since responders had a greater connectivity with the default mode network than non-responders, which is postulated to increase the threshold for seizure propagation. Other studies identified patient-specific tractography associated with seizure reduction [235] or found that non-invasive functional connectivity with MEG [186] may be a candidate to predict neurostimulation effectiveness. These studies are very promising, but distinguishing responders from non-responders after starting treatment is different from predicting optimal neurostimulation treatment beforehand. Prospective clinical studies with large patient groups who undergo VNS, DBS or CS are needed to find which biomarkers can be used to predict best stimulation therapy for the individual patient.

Biomarkers for optimization of stimulus parameters

Besides the challenge of finding the optimal stimulation site, how to optimize stimulation parameters for neurostimulation therapy is still unclear. We do not yet have a detailed understanding of the neuronal effects that result from different types of stimulation therapy. While neurostimulation therapy has potential to treat patients with drug-resistant epilepsy, understanding how different stimulation parameters affect neuronal activity is important for optimizing such therapies. Since electrical stimulation has a very large parameter space, with variables such as polarity, frequency, charge, current intensity, pulse width and stimulus duration, there is a wide range of settings to conduct neurostimulation therapy. This demonstrates the complexity of designing brain stimulation protocols to modulate brain activity in targeted ways to achieve best outcome on seizure frequency and severity.

Several studies have explored effects of some stimulation parameters commonly used in invasive neurostimulation. With high (145 Hz) frequency stimulation in the anterior nucleus of the thalamus, greater activation in the limbic region and default mode network and widespread cortical and subcortical deactivation was found compared to low (30 Hz) frequency stimulation [236]. Mohan et al. [237] measured broadband power spectra from 30-100 Hz and found that high-frequency stimulation (200 Hz) is more likely to increase broadband power, and stimulation at low frequencies (10 Hz) suppresses this broadband power. These effects were highly affected by the distance of the stimulation site to white-matter tracts. Another study [238] examining evoked neural responses to 400 ms trains of 10-400 Hz electrical stimulation ranging from 0.1 to 10 mA, found that the peak amplitude of response waveforms increased until ~100 Hz after which it plateaus, and it increased linearly with current intensity. Although these studies analyzed effects of some stimulation

parameters, this is only a very small fraction of the large parameter space that could be used for stimulation.

Another parameter that can be varied, is the modality in which stimulation is applied: open-loop or closed-loop stimulation. In **Chapter 5**, we reviewed these two modalities. Open-loop stimulation seemed to be more effective, but this is probably biased by a lower number of patients, compared to the studies applying closed-loop stimulation. The question remains what modality is most effective, and why. Two studies demonstrated reduced spike-wave-discharges in a genetic absence model in rats [193] or suppression of seizure-like activity in hippocampal brain slices [194] with closed-loop stimulation that were not observed with open-loop stimulation. A recent study by Scheid et al. [232] found that the amount of stimulation energy for a transition to a seizure-free state is smallest at seizure onset. During propagation and termination state of a seizure, more energy is required to counteract the natural ictal progression, indicating that closed-loop stimulation might be beneficial over open-loop stimulation. Open-loop stimulation seemed more effective than closed-loop stimulation in a rodent model, but this could also be due to the higher number of stimuli with open-loop stimulation [10]. Rolston et al. [24] postulated that because of the brain's plasticity and likely adaptive response to stimulation, a closed-loop stimulation protocol that adapts to changes in neural activity may be more effective than rigid open-loop stimulation [23,26,239]. In the early feasibility study described in **Chapter 7**, we applied closed-loop stimulation. Recently, we changed one patient from closed-loop to open-loop stimulation and she is seizure-free since this change. This suggests that some stimulus parameters in combination with the closed-loop modality were effective in some patients, but not in others [6,226]. The SOZ was located in the primary sensorimotor cortex in all patients, which suggests a more or less homogenous patient group. This indicates that choosing the modality of stimulation is not straightforward, and it is even possible that stimulation parameters and modality should vary depending on the current brain state [240]. It is therefore important to tailor therapeutic neurostimulation instead of expecting one stimulation parameter set that fits all individuals.

It is not feasible to explore the entire stimulation parameter space with each patient and characterize the response to stimulation, given the fact that we need to monitor the effect of stimulation on seizure frequency and severity for several weeks to months. A better solution would be to develop patient-specific computational models of the brain's response to electrical stimulation with e.g. neural mass models to predict the effect of a certain stimulation parameter set in advance [237,241]. These models also need to identify whether stimulus parameters are independent variables or that these parameters interact with each other resulting in different effects on brain regions.

Seizure diaries

In DBS therapy for tremor or Parkinson's disease, the effect of stimulation is observed almost immediately. In epilepsy patients, the effect is defined by a significant seizure frequency reduction over time. Seizure diaries are used in general to monitor seizure frequency and evaluate effective treatment for epilepsy. It is an established fact [242] that these diaries are very subjective and inaccurate: seizures are often either over- or underreported. This makes it very difficult to evaluate effectiveness of treatment. Currently, there are many developments to monitor seizure activity at home. Some examples are ear-electrodes [243–246], and intracranial EEG measurements [166,170,247,248]. Home-based monitoring, based on (intracranial) EEG, could also facilitate monitoring subclinical seizures. With epilepsy treatment, sometimes only the bilateral tonic-clonic seizures are suppressed, and focal seizures are still present. Having insight in those focal seizures could help us to further optimize treatment. Furthermore, home-based monitoring could also increase our insight in the effect of subclinical seizures and interictal epileptiform discharges on cognition, quality of life and participation in society. A recent study [249] showed an association between interictal epileptiform discharges and word-finding problems, suggesting that these discharges might be treated as well to minimize the effect of epilepsy on cognition. Home-based monitoring in combination with questionnaires on quality of life and participation in society could help us optimize treatment in the individual patient.

These methods to monitor seizure activity do not change the fact that it takes long to optimize stimulus parameters, since effect is defined by seizure frequency reduction over time. Seizures are usually too infrequent for parameters to be optimized in a clinical setting. Furthermore, seizure frequency fluctuates over time which requires long-term monitoring to evaluate effectiveness [250]. This makes seizures an impractical marker for treatment optimization.

The trajectory of optimizing stimulus parameters may take months to years, making this a very insecure period for the patient. It is therefore important to find good surrogate markers, e.g. events that are more readily available than seizures and correlates reliably with seizure frequency or severity [9], to predict potentially effective stimulation parameters. Many electrophysiological markers of epilepsy are potential candidates as surrogate marker: fast ripples, interictal spikes [162], preictal states, broadband power spectra [9]. When treatment-induced changes in a surrogate marker accurately correlates with seizure frequency or severity, the trajectory of optimizing stimulation parameters is enhanced, as the surrogate marker enables more frequent assessment of efficacy.

In **Chapter 6**, we investigated interictal epileptiform discharges and spectral

power as surrogate markers and found that interictal spikes could be modulated by SPES, when there is a connection between the stimulus pair and the response electrode. We also observed that this change in number of interictal spikes was only temporary, with a duration of 2s. Changes in neuronal activity can outlast the termination of stimulation by hours or days (defined as plastic changes [9]), and this might complicate the effect of other tested stimulus parameter sets on brain activity.

Heterogenous patient population

The studies in this thesis were executed in patients with focal, drug-resistant epilepsy. The patients' backgrounds varied with regard to anti-seizure medication, underlying pathologies and duration since epilepsy debut, all of which might lead to potential biases. Moreover, implantation plans were designed based on the patient-specific presumed location of epileptogenic tissue. This results in heterogeneous sampling of brain areas and heterogeneous electrical stimulation. Since intracranial electrocorticography has a limited spatial resolution, effects of stimulation on brain tissue, that is not covered by electrodes, is missing. In the studies described in this thesis, only subdural electrode grids were implanted. Therefore, we were not able to analyze effects of stimulation on deeper structures i.e. the thalamus, which is an important target for DBS in epilepsy patients. Furthermore, we had to reduce current intensity in the primary sensorimotor cortex to avoid twitches or sensations. This could have introduced biases because other regions may react differently to stimulation.

Challenges and opportunities with open science

Discovering and validating robust biomarkers for optimal stimulation site and stimulation parameters, is challenging due to the heterogeneity of the patient population with epilepsy, non-standardized clinical methods, and limited access to centralized clinical data, including outcome measures and medication regimens [233]. A large sample size is needed to take this heterogeneity into account. In the last decade, more effort is put into unifying data to enable analyses on large datasets [123]. The human connectome with fMRI data from 1000 patients has been used successfully in reporting a difference in clinical outcome with DBS-therapy when there was a stronger connection between the ANT and the seizure foci [251]. This study is one of the examples that could not have been executed when this data had not been shared on such a large scale.

In Chapter 8, we proposed a pipeline to preprocess intracranial EEG data. We also initiated an electronic data capture to collect medical data of all epilepsy surgery patients from the UMCU. With this large dataset, we can obtain more insight in how to optimize epilepsy surgery and which patients are at risk to develop adverse effects

after epilepsy surgery. In the future, this dataset might also facilitate the development of new treatment options.

However, analysis on large datasets from different centers must be handled carefully. Interpretation and context of medical reports might be missing. The International League Against Epilepsy (ILAE) has revised concepts, terminology, and approaches for classifying seizures and forms of epilepsy in 2010 and 2014 [252,253] and finalized these concepts in 2017 [254]. Marginal differences in defining seizure types could exist in populations included in datasets before and after 2010-2017. Synthesizing effects may be difficult since classification of clinical outcomes can be defined based on either the Engel classification or the ILAE classification [255]. Furthermore, association studies based on large datasets are commonly misinterpreted as demonstrating causal relationships [256]. In order to ensure a high quality of patient care, analysis of big data must be accompanied by clear plausibility checks, an evaluation of the likely effects of the findings for clinical practice and clear recommendations for clinical application.

Conclusion

In this thesis, we used electrocorticography (ECoG) to study properties of effective connectivity in brain networks. Epileptogenic tissue had a higher density of effective connections, with only limited connections towards this region. Under anesthetics, the number of connections decreased, but important nodes, with high indegree or outdegree, remained relatively important. The transmission speed between the stimulation site and the response electrode in which an evoked potential was observed increased with age, indicating that age might be taken into account when investigating brain networks and waveforms of evoked potentials. We observed neuromodulatory effects when SPES was applied in a stimulus pair with a connection to the epileptogenic region. We used this characteristic of effective connectivity in brain networks to localize potential stimulation sites for cortical network stimulation therapy in epilepsy patients and reviewed studies applying closed-loop and open-loop electrical stimulation therapy. These studies were all implemented in an early feasibility study in which we applied closed-loop cortical network stimulation therapy in five epilepsy patients. One major challenge is to find predictive biomarkers which predict optimal neurostimulation therapy and facilitate optimization of stimulation parameters without trial-and-error as is clinical practice nowadays. In the last chapter, we demonstrate a pipeline to process raw intracranial EEG data towards a standardized data structure. Open science and sharing data might help in executing large scale studies to find those predictive biomarkers.

APPENDICES

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Samenvatting | Dutch summary

Patiënten met epilepsie uit de primaire sensorimotor cortex hebben vaak invaliderende aanvallen die moeilijk te behandelen zijn met de standaard behandelmethodes zoals anti-epileptica en epilepsiechirurgie. Het gebied waar deze aanvallen ontstaan, kan goed gelokaliseerd worden vanwege de semiologie tijdens het begin van de aanval. Epilepsiechirurgie leidt echter zelden tot aanvalsvrijheid, omdat er bij resecties vaak maar een deel van het epileptogene weefsel wordt weggehaald om postoperatief functieverlies te voorkomen. Het feit dat het gebied van aanvalsbegin goed gelokaliseerd kan worden, maakt gerichte elektrische neurostimulatie mogelijk, maar directe elektrische stimulatie in dit gebied zou ook effect kunnen hebben op de motoriek.

Het doel van deze thesis was om een basis te leggen voor een nieuwe behandelmogelijkheid met corticale netwerk *closed-loop* elektrische stimulatie voor patiënten met epilepsie afkomstig uit de primaire sensorimotor cortex.

Deel 1: karakteristieken van effectieve connectiviteit in hersennetwerken

Een eerste stap voordat *closed-loop* elektrische stimulatie in een corticaal netwerk klinisch kan worden toegepast, is om meer inzicht te verkrijgen in deze corticale netwerken in het brein. Eén methode om effectieve connectiviteit in de hersenen te onderzoeken, is door *Single Pulse* Elektrische Stimulatie (SPES) toe te passen op twee naast elkaar gelegen elektrodes en de cortico-corticale opgewekte potentialen (CCEP) te evalueren, die zijn opgewekt door stimulaties op andere elektrodes op het subdurale elektrode grid. Eerdere studies hebben laten zien dat er een netwerkverbinding is tussen het stimulatiepaar en de responsieve elektrode, maar er is nog weinig bekend over deze netwerken onder verschillende condities en of deze netwerken bruikbaar zijn voor de selectie van een stimulatieplek voor *closed-loop* corticale netwerk elektrische stimulatie therapie. Hoofdstuk 2 verkent de verschillen in karakteristieken van het effectieve corticale netwerk in en buiten het epileptogene gebied. We analyseerden de *indegree*, *outdegree* en *betweenness centrality*, het percentage van bidirectionele, ontvangende en activerende verbindingen en het percentage verbindingen naar (non-)epileptogeen weefsel. Elektrodes op epileptogeen weefsel hadden hogere waardes voor *in*- en *outdegree.* We vonden geen verschil voor de *betweenness centrality*. We vonden ook meer bidirectionele en minder ontvangende verbindingen in het epileptogene

weefsel. Het epileptogene weefsel leek een hogere dichtheid aan verbindingen met zichzelf te hebben, en slechts weinig input van non-epileptogeen weefsel. Aan de ene kant gaven deze algemene resultaten mogelijkheden voor het afbakenen van het epileptogene gebied, omdat het netwerk in het epileptogene weefsel op een andere manier is georganiseerd. Aan de andere kant geeft dit mogelijkheden voor elektrische stimulatie therapie, omdat verbindingen naar het epileptogene gebied in kaart gebracht kunnen worden.

De resultaten in Hoofdstuk 2 zijn verkregen door SPES toe te passen in de wakkere patiënt, tijdens de klinische evaluatie voor epilepsiechirurgie. Het is echter onbekend hoe deze netwerken veranderen tijdens epilepsiechirurgie onder anesthesie. Deze informatie is relevant als we een stimulatieplek willen definiëren in de operatiekamer, als de neurostimulator wordt geïmplanteerd. In **Hoofdstuk 3** worden de effecten van anesthesie op effectieve connectiviteit onderzocht. Bij zes patiënten wordt SPES uitgevoerd als de patiënt wakker is, en als de patiënt onder narcose is tijdens de operatie waarbij subdurale elektrode grids worden geëxplanteerd. De netwerk topologie bleef vergelijkbaar in beide situaties: stimulatieparen met een hoge *outdegree* tijdens waak wekten minder CCEPs op onder narcose, maar hadden nog steeds een hoge *outdegree* vergeleken met de andere stimulatieparen onder narcose. Responsieve elektrodes met een hoge *indegree* tijdens waak, hadden nog steeds een relatief hoge *indegree* onder narcose, ook al was het absolute aantal opgewekte CCEPs in deze elektrodes lager.

In **Hoofdstuk 4** pasten we SPES toe bij 74 patiënten met een leeftijd tussen de 4-51 jaar. Met de opgewekte CCEPs berekenden we de transmissiesnelheid tussen en binnen verschillende hersenkwabben door de latentie te delen door de lengte van de onderliggende wittestofbanen. De transmissiesnelheid nam toe met leeftijd. Dit is belangrijke informatie als we accurate computationele modellen van hersennetwerken willen gebruiken om een potentiële stimulatieplek te bepalen en wanneer we zouden willen voorspellen welke stimulatieparameters het meest effectief zouden kunnen zijn in de individuele patiënt. Daarnaast werd het aantal verbindingen niet beïnvloed door leeftijd. Dit wekt de suggestie dat we verbindingen naar epileptogeen weefsel in kaart kunnen brengen bij patiënten met verschillende leeftijden. Dit fundamentele onderzoek legt de basis om eigenschappen van veelbelovende stimulatieplekken voor corticale netwerk elektrische stimulatie verder te onderzoeken.

Deel 2: neurostimulatie als behandeling voor epilepsiepatiënten

In deel 2 onderzoeken we therapeutische neurostimulatie voor patiënten met epilepsie. **Hoofdstuk 5** bespreekt alle studies, gepubliceerd tussen 1990-2017, met corticale

elektrische stimulatie in een neocorticaal aanvalsfocus met een geïmplanteerd apparaat. Zowel *open-loop* (in totaal werden 21 patiënten geïncludeerd) als *closed-loop* stimulatie (in totaal 256 patiënten) werd toegepast. Met *open-loop* stimulatie werden elektrische stimuli continu of volgens een cyclisch patroon (bijvoorbeeld 1 minuut aan, 5 minuten uit) toegepast. Met *closed-loop* stimulatie werden elektrische stimuli alleen toegepast wanneer een bepaald patroon werd gedetecteerd (zoals aanvalsonset of interictale piekpatronen). Patiënten die *open-loop* stimulatie kregen, hadden indrukwekkende (72-100%) afnames in aanvalsfrequentie. Patiënten die *closed-loop* stimulatie kregen, hadden een vermindering van aanvalsfrequentie van 44% na 1 jaar, en 53% na 2 jaar. Alhoewel de resultaten in de *open-loop* stimulatie studies veelbelovend zijn, zou er sprake kunnen zijn van een publicatie bias omdat slechts 21 patiënten deze vorm van stimulatie ontvingen. **Hoofdstuk 6** onderzoekt of we tijdelijke effecten van SPES op interictale activiteit kunnen gebruiken als surrogaatmarker voor langdurige neuromodulatie behandeling. We vonden meer neuromodulatie als de stimulatieplek verbonden was met het epileptische gebied. Meer neuromodulatie betekende hierbij dat er een grotere verandering was in het aantal interictale ontladingen, of een afname in breedbandige power. Dit betekent dat SPES gebruikt zou kunnen worden om een potentiële stimulatieplek te bepalen met effect in het epileptogene gebied.

Met de kennis die we verkregen hebben in de vorige hoofdstukken, waren we in staat om een klinische studie uit te voeren. Deze staat beschreven in **Hoofdstuk 7**. Hierbij pasten we *closed-loop* corticale netwerk elektrische stimulatie toe bij vijf patiënten met epilepsie die ontstond in de primaire sensorimotor cortex.

Tijdens de intracraniele grid monitoring periode werd er geconcludeerd dat het epileptogene gebied in de eloquente motor cortex lag en dat epilepsiechirurgie niet mogelijk zou zijn zonder het induceren van functieverlies postoperatief. We bepaalden een stimulatieplek buiten de primaire sensorimotor cortex met een verbinding naar het epileptogene gebied. We implanteerden een subdurale strip op de stimulatieplek, en een strip op het epileptogene gebied. We verzamelden electrocorticografische data van aanvallen en optimaliseerden een lineair discriminant algoritme om aanvallen van elke patiënt te detecteren. Daarna pasten we elektrische stimulatie toe als een aanval werd gedetecteerd. Eén jaar na implantatie van de neurostimulator was de aanvalsfrequentie afgenomen met gemiddeld 54% (26-77%) zonder de motoriek te beïnvloeden. Deze studie is een *proof of concept* dat *closed-loop* corticale netwerk stimulatie in staat is om de aanvalsfrequentie te verminderen zonder de motoriek aan te tasten. In de komende jaren zullen we de stimulatieparameters blijven aanpassen om verdere afname van aanvalsfrequentie te verkrijgen.

Deel 3: transitie naar open wetenschap

In het afgelopen decennium is open wetenschap steeds belangrijker geworden. Dit wordt weergegeven in de FAIR principes. Dit betekent dat data vindbaar, toegankelijk, compatibel en herbruikbaar moeten zijn. Als meer data volgens deze principes beschikbaar wordt gesteld, zou dit de vooruitgang in medische uitvindingen kunnen versterken en dit kan patiënten weer ten goede komen. Eén datastructuur die veel gebruikt wordt in de neurowetenschappen is de *Brain Imaging Data Structure* (BIDS). Veel voorbewerking is nodig om de data zo te structureren dat het gemakkelijk bruikbaar is voor een grote groep leden van de neurowetenschappelijke gemeenschap. In **Hoofdstuk 8** beschrijven we een pijplijn hoe klinische intra-operatieve en langdurige intracraniële EEG data in deze BIDS structuur kan worden georganiseerd. We delen ook praktische voorbeelden van twaalf patiënten om aan te tonen hoe intracranieel EEG omgezet kan worden naar BIDS. Om verder deel te nemen aan de open-wetenschap-beweging hebben we data beschikbaar gemaakt op openneuro.org van de onderzoeken uit de **Hoofdstukken 3**, **4** en **6**.

We concluderen dat we in deze thesis de basis hebben gelegd voor corticale netwerk *closed-loop* elektrische stimulatie. Ten eerste hebben we SPES toegepast en de eigenschappen van effectieve connectiviteit van hersennetwerken onderzocht. We vonden dat het corticale netwerk anders georganiseerd is in het epileptogene gebied, en dat dit netwerk binnen en tussen verschillende hersenkwabben sneller wordt met leeftijd. Daarnaast vonden we dat dit netwerk slechts marginaal verandert onder anesthesie: we vonden minder verbindingen, maar belangrijke knooppunten bleven relatief belangrijk onder anesthesie. Dit geeft ons mogelijkheden om de effectieve connectiviteit van hersennetwerken tijdens operaties te bepalen. We gebruikten SPES ook om tijdelijke effecten van stimulatie op interictale activiteit te onderzoeken. We vonden dat deze neuromodulatoire effecten vaker voorkwamen als er een verbinding was tussen de stimulatieplek en de elektrode op het epileptogene weefsel. Dit gaf ons een startpunt om veelbelovende stimulatieplekken voor neurostimulatie behandeling te bepalen. Deze onderzoeken leidden uiteindelijk tot de initiatie van een klinische studie waarbij we corticale netwerk stimulatie toepasten met als doel om de aanvalsfrequentie te verminderen bij patiënten met epilepsie uit de primaire sensorimotor cortex. Eén jaar na implantatie van de neurostimulator was er een gemiddelde afname in aanvalsfrequentie van 54% (26-77%). Dit laat zien dat deze therapie veelbelovend is, maar dat er ook nog stappen te zetten zijn om de aanvalsfrequentie verder te verminderen.

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This thesis

1. **van Blooijs D***, Vassileva A*, Leijten F, Huiskamp G. Neocortical electrical stimulation for epilepsy: Closed-loop versus open-loop. Epilepsy Res. 2018 Mar;141:95-101. doi: 10.1016/j.eplepsyres.2018.02.010.
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10. Van den Boom M, Gregg N, Ojeda Valencia G, Lundstrom B, Miller K, **van Blooijs D**, Huiskamp G, Leijten F, Worrell G, Hermes D. ER-detect: optimized preprocessing of intracranial electrophysiological BIDS data and robust detection of early responses in single pulse electrical stimulation. under review

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1. **van Blooijs, D.**, & Leijten, F. (2019). Stimulatie van de sensorimotorische cortex: Van functiemapping tot behandeling. Epilepsie, Periodiek Voor Professionals, 17(1), 13–16. https://doi.org/10.54160/epilepsie.11245
2. **van Blooijs, D.** (2021). Rationele extra-eloquente closed-loop corticale stimulatie. Epilepsie, Periodiek Voor Professionals, 19(1), 14–16. https://doi.org/10.54160/epilepsie.11033

Curriculum Vitae

Dorien van Blooijs was born on July 2nd, 1989 in Eindhoven, the Netherlands. At a young age, she was already enthusiastic about science and helped her classmates with their math, physics and chemistry during high school. After a biology class about cardiology, she considered Medicine being a great study for her, but she thought she would miss math and physics. Therefore, she started with the bachelor Technical medicine at the University of Twente, Enschede in 2008. In 2011, she initiated a charity project called "Happietaria". Happietaria was a pop-up restaurant that opened its doors for one month. All profit (€78000,-) was given to Fairtrade to help farmers gain a normal living and support their villages. In 2012, she started with the master Medical Signaling. After several internships in Utrecht (Clinical Neurophysiology), Rotterdam (Cardiophysiology), Nijmegen (Neonatology) and Eindhoven (Philips), she concluded that she was most passionate about the brain and particularly the fact that so much about the brain is still unknown. After successful completion of her master thesis in 2015, she continued working as a technical physician in the Clinical Neurophysiology department at the UMC Utrecht.

In 2016, she and her supervisor dr. Frans Leijten received a grant from EpilepsieNL (WAR 2017-07) to investigate closed-loop cortical network electrical stimulation as a treatment for patients with epilepsy arising from the primary sensorimotor cortex, of which this PhD thesis is the result. Curious to learn more about electrical stimulation as a treatment for epilepsy patients, she spent four months (June-September 2021) at dr. Dora Hermes' lab at Mayo Clinic, Rochester, Minnesota. Together, they analyzed the physiological responses to electrical stimulation in intracranial EEG data of epilepsy patients (van Blooijs & van den Boom et al. Nature Neuroscience 2023). This paper was awarded with the UMCU publication prize 2023. Dorien was also awarded with the Trainee Professional Development Award by the Society for Neuroscience, and selected for the PhD Career Boost Program at the UMC Utrecht.

From the pilot study with closed-loop cortical network stimulation, she learned that optimizing stimulus parameters involves a lot of trial and error and this is a very time-consuming process. In 2022, she received another grant (WAR 2023-06) from EpilepsieNL to continue her research on cortical electrical stimulation with a specific focus on finding ways to predict what stimulus parameters would be optimal in the individual patient. Since October 2021, she is working as a technical physician at Stichting Epilepsie Instellingen Nederland (SEIN) in Zwolle. She aims to increase our knowledge of stimulation therapy for individuals with epilepsy, to optimize home-based monitoring to evaluate seizure activity and to implement this knowledge in clinical practice. The latter was also acknowledged with a grant from ZonMw (FP-923) in 2023. She currently lives in Leusden with her husband Gerrit, their daughters Milou and Sophia and their cat Charlie.