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Improving the presurgical evaluation of patients with epilepsy using MEG

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ENGLISH SUMMARY

Around 0.1% of the population world-wide is affected by epilepsy (Banerjee et al., 2009; Forsgren et al., 2005; Sander, 2003). The first treatment choice is anti-epileptic drugs, but those are not effective in one-third of the patients (Kwan et al., 2010; Sander, 2003). For those drug-resistant patients, epilepsy surgery is a potent treatment option if the seizures are thought to have a focal origin. Before surgery, every patient undergoes several investigations, including structural and functional imaging and neurophysiological investigations, which together constitute the presurgical evaluation. The aim of the presurgical evaluation is to 1) define the outline of the resection area and 2) localize eloquent cortex, which should be spared. If a patient achieves seizure freedom after surgery, per definition the resection area was at the correct location and is defined as the epileptogenic zone (Lüders et al., 2006). However, epilepsy surgery does not result in seizure freedom in one-third of the patients (Englot et al., 2015b; Jobst and Cascino, 2015; Spencer and Huh, 2008).

The **aim** of this dissertation was to improve surgery outcome by improving the localization of the epileptogenic zone. For this purpose, we evaluated the value of non-invasive magnetoencephalography (MEG) recordings and invasive stereotactic electroencephalography (SEEG) recordings in the interictal period (the time between seizures).

A first step was to make an overview of all MEG recordings that were performed at our tertiary referral center in recent years (starting in 2010). **Chapter 2** describes the characteristics of the patient population in whom an MEG was recorded at our center as part of their presurgical evaluation. The aim was to evaluate the success of MEG in localizing epileptiform activity using the current clinical standard tools (equivalent current dipole (ECD) analysis). MEG was able to localize epileptiform activity in the majority of patients (78%). However, a considerable part of the recordings (12%) contained only normal activity, i.e. they did not display any abnormalities (not even focal slow activity) and therefore there were no epileptiform discharges to be localized. The results showed that the ability of MEG to localize epileptiform abnormalities could not be predicted beforehand on the basis of patient characteristics. Therefore, MEG should not be withheld in any patient in the presurgical evaluation for refractory epilepsy, as MEG can potentially add information even in patients with a complex etiology. The patients in whom MEG could detect but not localize epileptiform abnormalities had inconclusive EEG and MRI findings and non-epileptiform MEG abnormalities. Those patients stand to benefit the most from new or improved localization methods.

A first localization method, kurtosis beamforming, was tested in **Chapter 3**. Kurtosis beamforming automatically localizes regions with time-series that show positive excess

kurtosis, which indicates the presence of spikes (interictal epileptiform abnormalities). We found that kurtosis beamforming cannot replace the standard ECD analysis, but it complements it by detecting epileptiform activity that was missed in the visual analysis or in cases with unreliable localization through ECD analysis. Therefore, kurtosis beamforming should be integrated with existing clinical protocols to assist in localizing the epileptogenic zone. However, the method relies on the presence of spikes in the recording similarly to ECD analysis.

Network theory has been suggested as a framework to obtain alternative measures of the epileptogenic zone even in the absence of clear epileptiform discharges. **Chapter 4** focused on network hubs as a possible indicator of the epileptogenic zone. Hubs play an important role in epilepsy and might be located inside or close to the epileptogenic zone, from where seizure activity can spread to the rest of the brain. High hub values were able to localize the epileptogenic zone in the majority of patients, suggesting that hubs are located close by the epileptogenic zone. These results show that non-invasive MEG recordings contain information about the location of the epileptogenic zone even in the absence of epileptiform activity.

The next question was, whether the hubs are located in the center or nearby the epileptogenic zone. To answer that question in **Chapter 5**, we placed so-called MEG virtual electrodes in the irritative zone (the area with interictal epileptiform activity as localized by MEG ECD analysis). Virtual electrodes can be placed in user-defined positions in the brain to reconstruct activity from a specific region. The virtual electrode analysis showed that hubs are not located right in the center but nearby the irritative zone, and that interictal spikes and high frequency oscillations (HFOs) negatively correlate with hub status. These findings suggest that hubs are not accurate indicators of the epileptogenic zone itself, but might indicate a larger area surrounding it. The hypothesis about hubs located remotely from the epileptogenic zone opens new possibilities for surgery in patients in whom the epileptogenic zone is located within eloquent cortex.

Chapter 6 extends the search of a localization marker for the epileptogenic zone by including more measures and more patients. We found that most measures (slow activity, high connectivity and network hubs) identified the resection area when considering all patients (disregarding surgery outcome). However, when differentiating between surgery outcome (seizure-free versus not seizure-free patients), the measures did not localize the epileptogenic zone (the resection area in seizure-free patients). Additionally, differences at the group level were more pronounced than at the individual level. Machine learning tests hypotheses at an individual level, which is important in tailoring the surgical approach on a patient-by-patient basis irrespective of its etiology. The results demonstrate that metrics derived from interictal MEG recordings correspond to expert consensus derived from



various presurgical evaluation modalities.

Chapter 7 employs MEG virtual electrodes to zoom in on the hippocampus. The hippocampus is embedded deep in the temporal lobe, and activity from deep structures is difficult to detect with MEG. We showed that virtual electrodes enable the detection of spikes arising from the hippocampus, even in cases where they cannot be easily identified in sensor space. Virtual electrodes can be used in clinical analysis to detect spikes in deep structures, as well as to probe areas that are suspect of epileptiform activity.

In **Chapter 8**, virtual electrodes were placed at the same locations as the contact points of depth electrodes. This allowed for a direct comparison between MEG recordings and SEEG recordings. We found that the seizure onset zone was characterized by slow activity and high connectivity by both measurement techniques. Furthermore, both modalities showed similar spectral and functional connectivity properties, but not similar network properties. This implies that MEG virtual electrodes can be used to investigate specific hypotheses regarding the area with epileptiform activity beforehand and thereby support the planning of SEEG placement.

In **conclusion**, MEG is a valuable and non-invasive part of the presurgical evaluation because it can reveal information about the location of the epileptogenic zone. The use of virtual electrodes makes the application of MEG versatile and enables the investigation of both entire brain networks as well as hypothesis-driven subsets or regions. However, the application of network theory did not show consistent results in the search for markers of the epileptogenic zone so far. Information is contained in interictal periods, but network theory is possibly more suited for group comparisons than for localization purposes in individual patients. Therefore, taking a step back and answering questions about markers for seizure freedom might lead to better hypotheses for finding a network-based localization marker for the epileptogenic zone in the future. Additionally, machine learning and individualized computer models enable the testing of several markers on a patient-by-patient basis. Finally, network theory can lead to a better understanding of the mechanisms behind epilepsy and seizure freedom, where the epileptogenic zone is seen as part of a wider epileptogenic network.