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Brain areas with epileptic high frequency oscillations are functionally isolated in MEG virtual electrode networks

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HIGHLIGHTS

- Virtual electrodes enable a non-invasive view of the irritative zone.
- The irritative zone does not function as a hub but is functionally isolated in the interictal state.
- Functional connectivity is high within the irritative zone.

ABSTRACT

Objective: Previous studies have associated network hubs and epileptiform activity, such as spikes and high frequency oscillations (HFOs), with the epileptogenic zone. The epileptogenic zone is approximated by the area that generates interictal epileptiform activity: the irritative zone. Our aim was to determine the relation between network hubs and the irritative zone.
Methods: Interictal resting-state MEG recordings of 12 patients with refractory epilepsy were analysed. Beamformer-based virtual electrodes were calculated at 70 locations around the epileptic spikes (irritative zone) and in the contralateral hemisphere. Spikes and HFOs were marked in all virtual electrodes. A minimum spanning tree network was generated based on functional connectivity (phase lag index; PLI) between all virtual electrodes to calculate the betweenness centrality, an indicator of hub status of network nodes.
Results: Betweenness centrality was low, and PLI was high, in virtual electrodes close to the centre of the irritative zone, and in virtual electrodes with many spikes and HFOs.
Conclusion: Node centrality increases with distance from brain areas with spikes and HFOs, consistent with the idea that the irritative zone is a functionally isolated part of the epileptic network during the interictal state.
Significance: A new hypothesis about a pathological hub located remotely from the irritative zone and seizure onset zone opens new ways for surgery when epileptogenic areas and eloquent cortex coincide.

1. Introduction

Epilepsy surgery in patients with refractory epilepsy is successful in two thirds of the patients (Englot et al., 2015; Jobst and Cascino, 2015; Wyllie et al., 1998). Presurgical evaluation is performed to outline the potential epileptogenic zone and eloquent cortex. Various non-invasive (e.g. electro- and magnetoencephalography (EEG/MEG), magnetic resonance imaging (MRI)) and invasive methods (e.g. intracranial grid EEG, depth electrodes) are used to record and find the source of epileptiform activity. MEG measures neural activity directly and can record ictal and interictal epileptiform activity, such as spikes and focal slowing, to localize the irritative zone. The irritative zone is defined as the area of cortex that generates interictal spikes (Luders et al., 2006), and gives an indication of the location of the epileptogenic zone. The epileptogenic zone is based on post-surgical outcome and defined as the area that needs to be removed or disconnected to result in seizure freedom (Luders et al., 2006). The source location found by MEG recordings is often used to guide depth electrode placement and

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to plan surgical intervention (Agirre-Arrizubieta et al., 2014; Stefan et al., 2011).

High-frequency oscillations (HFOs) have been reported to be potential biomarkers of the epileptogenic zone (Bragin et al., 2010; Jacobs et al., 2012; Jirsch et al., 2006; Malinowska et al., 2014; Zijlmans et al., 2012). HFOs are characterised as at least four oscillations with an amplitude above baseline and a frequency of >80 Hz (Worrell et al., 2012). HFOs are more specific markers of the seizure onset zone than spikes (Jacobs et al., 2008; Melani et al., 2013) and they occur in smaller areas than spikes. The detection of HFOs is conventionally performed in intracranial EEG, but recent studies have reported HFOs in scalp EEG (Andrade-Valenca et al., 2011; Kobayashi et al., 2010) and MEG (Miao et al., 2014; van Klink et al., 2015; Xiang et al., 2009). The detection of HFOs requires a high sampling rate and low background noise. Van Klink et al. reported that HFOs were more readily identified in virtual electrodes than in physical MEG sensors (van Klink et al., 2015). Virtual electrodes refer to a spatial filtering approach (beamforming) that estimates the activity from a location within the brain on the basis of the extra-cranial MEG recordings (Hillebrand et al., 2005; Hillebrand and Barnes, 2005), resulting in an improved signal-to-noise-ratio.

Epilepsy is nowadays thought of as a network disorder, where the epileptogenic networks produce abnormal activity (ictal and interictal epileptiform activity, HFOs, and focal slowing), which may result in seizures (Kramer and Cash, 2012; Stam, 2014). The epileptogenic network consists of spatially distributed cortical and subcortical structures that are abnormally connected; it includes the seizure onset zone, the irritative zone, and the connections along which the seizures spread (Bartolomei et al., 2004,2001; Briellmann et al., 2004). Brain networks in epilepsy patients are disturbed and deviate from an optimal configuration (Douw et al., 2010; Horstmann et al., 2010; Ponten et al., 2007). Hubs are regions that play a central role in the network, for example because they are well-connected, and/or because much of the communication over the network goes through these nodes (Bullmore and Sporns, 2012; van den Heuvel and Sporns, 2013). Regions that normally function as a hub in brain networks are more likely to be abnormal in brain disorders (Crossley et al., 2014; Stam, 2014). Therefore, hubs are of particular interest in epilepsy. They are thought to play a central role in seizure generation, namely by enabling the spread of the epileptiform activity that arises in the seizure onset zone (defined as the area that initiates clinical seizures (Luders et al., 2006)) to the rest of the network (Bernhardt et al., 2011; Jin et al., 2015; Morgan and Soltesz, 2008). An indicator for hub status is betweenness centrality (Boccaletti et al., 2006). Invasive recordings (electrocorticography (ECoG) and depth electrodes) have shown that betweenness centrality is highest within brain areas that generate ictal and interictal epileptiform activity (Varotto et al., 2012), and that this correlates with the resection area in seizure-free patients (Wilke et al., 2011). In contrast, a study by van Diessen et al. using depth electrodes recordings during the interictal state, showed that contact points in the seizure onset zone had a decreased hub status compared to contact points outside the seizure onset zone (van Diessen et al., 2013). The opposing results could be due to methodological differences, as the studies differed in modality, patient population, connectivity measure, recorded state, and hub measure. Non-invasive studies have also found that the hub status of some regions differ in epilepsy patients compared to controls (Bernhardt et al., 2011; Jin et al., 2015; Liao et al., 2010; van Dellen et al., 2014; Zhang et al., 2011). However, there is no consensus (1) whether the hub status is higher or lower in patients compared to controls and (2) whether the hubs are located within or outside the epileptogenic zone. An fMRI study showed that interictal hub nodes differed between patients with idiopathic generalized epilepsy and controls, but both increased and decreased hub status in patients was reported (Zhang et al., 2011). In temporal lobe epilepsy, functional and structural MRI studies found the majority of abnormal (interictal and structural) hubs outside the temporal lobe (Bernhardt et al., 2011; Liao et al., 2010). In addition, a recent MEG study found the interictal hub in the hippocampus in left mesial temporal lobe epilepsy (mTLE) patients, whereas this was not the case for right mTLE patients (Jin et al., 2015). An MEG study by van Dellen et al. reported post-surgical decreases in betweenness centrality in regions close to the resection area, but only for patients with lesional epilepsy who became seizure free (van Dellen et al., 2014).

Taken together, both invasive and non-invasive recordings of structural and functional networks have found that (pathological) hubs play an important role in the epileptogenic network. However, it is as yet unclear whether the area that generates epileptiform activity itself functions as a hub or not. Does it function as a hub during the interictal state, from which activity can spread to the rest of the epileptogenic network, or is it functionally isolated to prevent spreading? The aim of our study was to determine the spatial relationship between network hubs and regions that generate interictal epileptiform activity. Do functional connectivity and betweenness centrality (as an indicator of hub status) increase or decrease with distance from the location of interictal epileptiform activity (i.e. spikes and HFOs)? A spatial correlation of hub status and location of interictal epileptiform activity would support the hypothesis that the irritative zone functions as a pathological hub from which epileptiform activity can spread. In this case, hub measures could be used as a non-invasive biomarker for the irritative zone. On the other hand, a spatial anticorrelation of hub status and the location of interictal epileptiform activity would be consistent with the idea that the irritative zone is kept functionally isolated, indicating that generation and spread of epileptiform activity happen by separate mechanisms.

2. Materials and methods

2.1. Patients

Twelve patients with refractory epilepsy had a clinical MEG recording in 2013 as part of their preoperative evaluation at the VU University Medical Center, Amsterdam, The Netherlands. The dataset has previously been published in van Klink et al. (2015). All patients had epileptiform activity in the MEG recording. Table 1 provides an overview of the patient characteristics, presurgical evaluation results, and surgery outcome. Written informed consent was obtained from patients or their caretakers prior to the MEG recording.

2.2. MEG acquisition

MEG recordings were obtained using a whole-head MEG system (Elekta Neuromag Oy, Helsinki, Finland) with 306 channels consisting of 102 magnetometers and 204 gradiometers.

The patients were in supine position inside a magnetically shielded room (Vacuumschmelze GmbH, Hanau, Germany). Typically, three datasets of 15 min each containing eyes-closed resting-state recordings were acquired for the identification and localization of interictal epileptiform activity. Paradigms for the localization of eloquent cortex, such as voluntary movements and somatosensory stimulation (see (Hillebrand et al., 2013)) were also recorded but not analysed in this study. The data were sampled at 1250 Hz, and filtered with an anti-aliasing filter of 410 Hz and a high-pass filter of 0.1 Hz. To localize the head position relative to the MEG sensors the signals from four or five