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Epilepsy surgery outcome and functional network alterations in longitudinal MEG: A minimum spanning tree analysis

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ABSTRACT

Seizure freedom after resective epilepsy surgery is not obtained in a substantial number of patients with medically intractable epilepsy. Functional neural network analysis is a promising technique for more accurate identification of the target areas for epilepsy surgery, but a better understanding of the correlations between changes in functional network organization due to surgery and postoperative seizure status is required. We explored these correlations in longitudinal magnetoencephalography (MEG) recordings of 20 lesional epilepsy patients. Resting-state MEG recordings were obtained at baseline (preoperatively; T0) and at 3–7 (T1) and 9–15 months after resection (T2). We assessed frequency-specific functional connectivity and performed a minimum spanning tree (MST) network analysis. The MST captures the most important connections in the network. We found a significant positive correlation between functional connectivity in the lower alpha band and seizure frequency at T0, especially in regions where lesions were located. MST leaf fraction, a measure of integration of information in the network, was significantly increased between T0 and T2, only for the seizure-free patients. This is in line with previous work, which showed that lower functional network integration in lesional epilepsy patients is related to higher epilepsy burden. Finally, eccentricity and betweenness centrality, which are measures of hub-status, decreased between T0 and T2 in seizure free patients, also in regions that were anatomically close to resection cavities. Our results increase insight into functional network changes in successful epilepsy surgery and might eventually be utilized for optimization of neurosurgical approaches.

Introduction

Epilepsy is common in patients with circumscribed brain abnormalities, such as primary brain tumors and mesiotemporal sclerosis. In a substantial number of patients, anti-epileptic drug treatment is ineffective (Berg, 2008; Duffau et al., 2002; Hildebrand et al., 2005; Picot et al., 2008). Many patients with medically intractable non-tumoral lesional epilepsy are referred to epilepsy surgery programs. The aim of these programs is to identify patients in whom it is possible to localize and remove the epileptogenic zone (EZ), i.e. the brain regions that need to be resected to achieve seizure freedom. This strategy succeeds in only 27–67% of these patients, depending on the specific histopathology of the lesion (Tellez-Zenteno et al., 2005). Although the primary aim of surgery in patients with brain tumors is the removal of the tumor, seizure reduction often is an important secondary aim (Chang et al., 2008). For both patient groups, seizure freedom is extremely relevant, as epilepsy is an important limiting factor for quality of life and cognitive functioning (Klein et al., 2003; Markand et al., 2000; Tellez-Zenteno et al., 2007).

The high prevalence of persistent seizures after epilepsy surgery demonstrates that the EZ is insufficiently identified and removed in these patients. The EZ is increasingly seen as an epileptogenic network instead of a localized cortical area, and removal of key regions in this network may increase success rates of epilepsy surgery (Kramer and Cash, 2012; Stam and van Straaten, 2012). Apart from the EZ, the functional organization of the brain network as a whole is disturbed in lesional epilepsy (Kramer and Cash, 2012). Overall, functional connectivity is increased particularly in the delta and theta frequency ranges (0.5–8 Hz) in MEG and EEG recordings, which is a hallmark of (tumor-related) epilepsy (Bettus et al., 2008; Douw et al., 2010a; Horstmann et al., 2010; van Dellen et al., 2012). However, network disturbances are not limited to this pathological increase in slow wave synchrony. The spatial organization or topology of functional neural

Abbreviations: EZ, epileptogenic zone; MEG, magnetoencephalography; MST, minimum spanning tree; PLI, phase lag index; SF, seizure free; POS, post-operative seizures.

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networks determines to what extent the network facilitates synchronization and the spreading of seizures (Dyhrfjeld-Johnsen et al., 2007; Percha et al., 2005; Varotto et al., 2012). The healthy functional brain network is characterized by a small-world topology, which is thought to be an optimal network topology that combines global integration with local specialization of highly interconnected areas (Bullmore and Sporns, 2009). This small-world topology is lost in lesional epilepsy and primary brain tumor patients (Bartolomei et al., 2006; Bosma et al., 2009; Horstmann et al., 2010), and in particular the loss of connections that integrate different functional regions or clusters correlates with seizure frequency (Douw et al., 2010b; van Dellen et al., 2012). Interestingly, functional connectivity and network characteristics are altered by neurosurgical resections, and such changes are related to postoperative cognitive performance (Douw et al., 2008; van Dellen et al., 2013a). However, so far, surgery-induced alterations in functional network characteristics have not been correlated to postoperative seizure status, which might provide valuable insights for more accurate identification of the target areas for epilepsy surgery.

For this study several choices were made for an approach that builds upon previous work. Firstly, most measures used to characterize networks of lesional epilepsy patients depend on the number of nodes and connection density of the network, hence a normalization strategy is needed. Unfortunately, the normalization approaches that are commonly used introduce their own biases (van Wijk et al., 2010). The use of minimum spanning tree (MST) network analysis provides a principled way to construct unique networks from neurophysiological data, which uses a fixed number of nodes and edges, and is independent of average coupling strength (Boersma et al., 2013). The MST is the subset of strongest connections in the network such that all network nodes are connected, without forming loops. It might represent a critical backbone of information flow in weighted networks (i.e. it contains with high probability all the shortest paths in the network; see Fig. 1 (Wang et al., 2009)).

The use of MST analysis also solves a second methodological concern. Functional connectivity analysis and the small-world model have proven to be a fruitful starting point for studies on brain network topology in lesional epilepsy, but they provide an incomplete representation of the networks, as they do not capture other network features such as the existence of so-called hubs (Stam and van Straaten, 2012). Several studies on electrocorticography (ECoG) recordings show that hub regions, which are highly connected regions with a central role in the network, seem to characterize the EZ (Ortega et al., 2008a; Varotto et al., 2012; Wilke et al., 2010). MST analysis allows for characterization of global integration of information and hubs in one holistic model (Fig. 2), and has been used to characterize ECoG and EEG recordings of epilepsy patients (Lee et al., 2006; Ortega et al., 2008b). These studies showed that networks of left-sided and right-sided mesiotemporal sclerosis patients are dissimilar, and suggested that the EZ is characterized by nodes with a high centrality in the MST.

Finally, previous studies were either based on spatially confined intracranial recordings (ECoG studies), or, in the case of most MEG/EEG

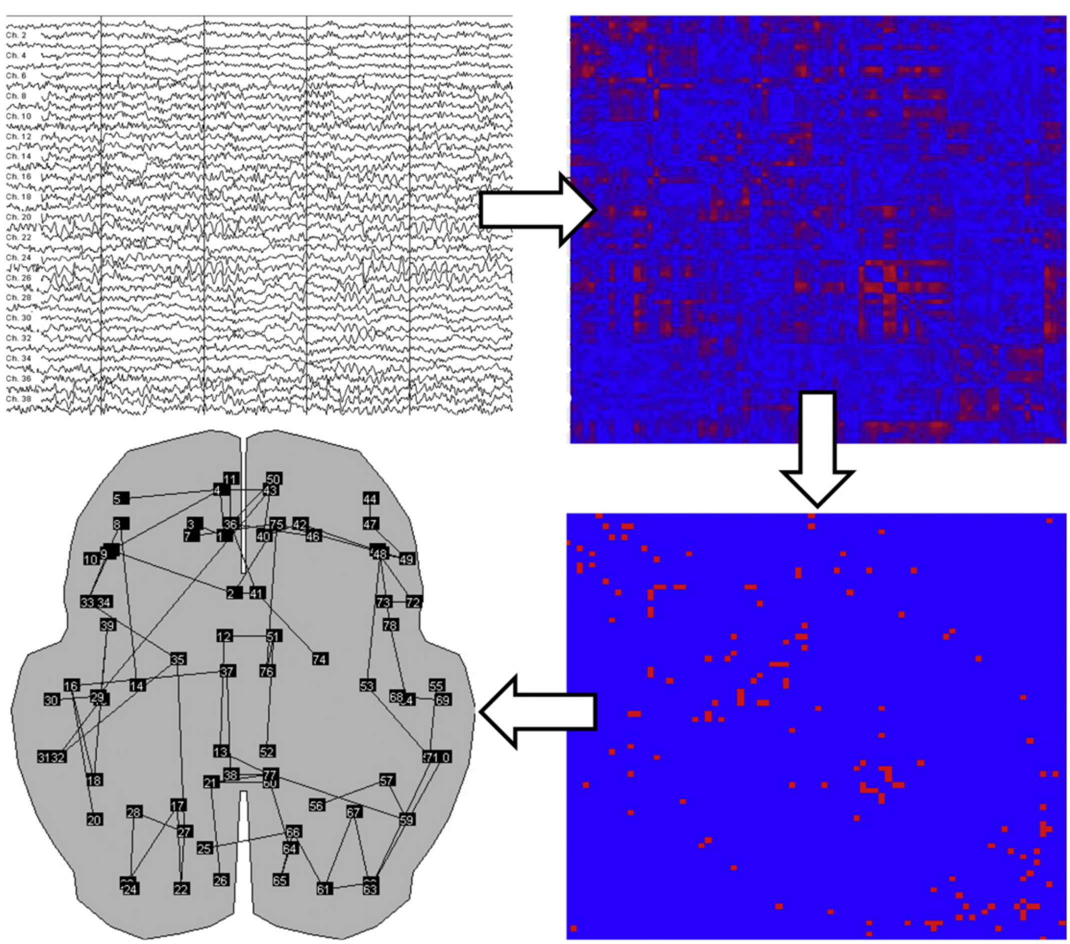

Fig. 1. Data analysis pipeline. Estimates of neuronal activity in 78 ROIs of the AAL atlas were obtained using an atlas-based beamformer (upper left). PLI values were calculated to quantify functional connectivity between every pair of ROIs, which are represented in an adjacency matrix (upper right). The minimum spanning tree was constructed from the adjacency matrix in order to obtain a unique sub-graph (lower right), which was then further analyzed in order to characterize the topology of the minimum spanning tree (lower left).