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Whole-brain analytic measures of network communication reveal increased structure-function correlation in right temporal lobe epilepsy

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ABSTRACT

The in vivo structure-function relationship is key to understanding brain network reorganization due to pathologies. This relationship is likely to be particularly complex in brain network diseases such as temporal lobe epilepsy, in which disturbed large-scale systems are involved in both transient electrical events and long-lasting functional and structural impairments. Herein, we estimated this relationship by analyzing the correlation between structural connectivity and functional connectivity in terms of analytical network communication parameters. As such, we targeted the gradual topological structure-function reorganization caused by the pathology not only at the whole brain scale but also both in core and peripheral regions of the brain.

We acquired diffusion (dMRI) and resting-state fMRI (rsfMRI) data in seven right-lateralized TLE (rTLE) patients and fourteen healthy controls and analyzed the structure-function relationship by using analytical network communication metrics derived from the structural connectome.

In rTLE patients, we found a widespread hypercorrelated functional network. Network communication analysis revealed greater unspecific branching of the shortest path (search information) in the structural connectome and a higher global correlation between the structural and functional connectivity for the patient group. We also found evidence for a preserved structural rich-club in the patient group. In sum, global augmentation of structure-function correlation might be linked to a smaller functional repertoire in rTLE patients, while sparing the central core of the brain which may represent a pathway that facilitates the spread of seizures.

1. Introduction

Characterization of the structure-function relationship in brain networks is crucial to the understanding of both normal and diseased brain organization. This relationship can be defined by correlating functional and structural connectivity (Honey et al., 2009). The complete set of structural or functional links between brain areas has been referred to as the structural or functional connectome (Sporns et al., 2005) and can be analyzed by graph theoretical measures (Achard et al., 2006; Sporns, 2013). Graph theory holds promise as a method to reveal pathological reorganization of brain networks (Fornito et al., 2015; Guye et al., 2010). When the network is altered in pathologies, localized structural changes in the brain are likely to result in complex direct and indirect functional alterations at various different scales and levels of integration.

Abbreviations: CSD, constrained spherical deconvolution; CSF, cerebrospinal fluid; dMRI, diffusion magnetic resonance imaging; FA, fractional anisotropy; FCA, analytic functional connectivity; FCD, functional connectivity dynamics; FOD, fiber orientation distribution; NBS, network based statistics; rsfMRI, resting state functional magnetic resonance imaging; rTLE, right temporal lobe epilepsy.

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This propagation of local changes through the network renders the structure-function relationship highly non-trivial. Here we study the network changes in temporal lobe epilepsy (TLE), whilst taking into account the complexity of indirect structure-function correlations (Damoiseaux and Greicius, 2009) by means of a graph analytic network communication approach (Goñi et al., 2014). TLE is now regarded as a pathology involving areas not only participating in a localized epileptogenic network (producing transient electrical abnormalities) but also having long-lasting large scale network effects over the whole brain (Bartolomei et al., 2001; Laufs, 2012; Spencer, 2002). These effects have been revealed and quantified mostly by in vivo MRI studies, accessing both the structural and the functional organization of the whole brain (Bernhardt et al., 2013).

Structural alterations of a priori brain subnetworks have been assessed in epileptic patients using graph analysis, finding widespread subcortical alterations in epileptic subnetworks (Bonilha et al., 2012). In contrast, a more global approach comparing whole brain structural connectivity between patients with bilateral TLE and controls identified a network of structural connectivity alterations in the temporal lobe distributed to different networks for left and right TLE (Besson et al., 2014). Substrates of these structural alterations are still debated, though studies employing post mortem histology in TLE show the presence of white matter damage, neuronal loss and gliosis both within (Thom et al., 2000, 2001) and beyond epileptogenic regions (Blanc et al., 2011), most likely caused by the propagation of recurrent epileptic seizures throughout the brain.

From a functional perspective, rsfMRI studies in epileptic patients reported various, widespread and complex patterns of increased and decreased functional connectivity, effecting key features of large scale networks such as the default mode network (Haneef et al., 2012; Liao et al., 2010; Pittau et al., 2012; Voets et al., 2012). Discrepancies in reported functional brain reorganization could be related to the broad range of methodological approaches used in these studies (e.g. whole brain network corrected analysis vs. a-priori ROI analysis), which make it difficult to reach a synthetic interpretation of these results (Centeno et al., 2014; Constable et al., 2013).

In epilepsy, modeling the brain as a graph can be of use in assessing the link between structural and functional connectivity (Bernhardt et al., 2013; Guye et al., 2008). Several recent studies have endeavored to combine structural and functional approaches in epilepsy (Chiang et al., 2015; Douw et al., 2015; Vaessen et al., 2014; Voets et al., 2012; Zhang et al., 2011). Function-structure relationship has been studied in the epileptic brain in generalized epilepsies (Zhang et al., 2011), frontal lobe epilepsy (Vaessen et al., 2014) and in TLE (Voets et al., 2012). While focusing only on limbic and pre-limbic structures Chiang et al. (2015) found decreased structural-functional relationship in TLE. Douw et al. (2015) observed higher anatomical between-module connectivity which correlated with default mode disintegration in TLE compared to a control group.

Structural parameters of brain networks such as Euclidian distance or the combination of more complex graph analytical metrics of network communication such as path length, search information and path transitivity have also provided good predictions of functional connectivity in the normal brain (Goñi et al., 2014). Considering a structural link in the context of its neighbors makes structure-function analysis more sensitive to accumulated small structural changes which trigger widespread functional connectivity changes across the network. As such, we hypothesize that these metrics could help to better characterize structural-functional reorganization in TLE, particularly in the context of epilepsy where dMRI tractography cannot grasp the full spectrum of structural change induced by the pathology. For example, gradual linear structural changes (secondary effects of both ictal and interictal epileptic phenomena) such as demyelination may not be visible to probabilistic tractography, but by their distributed effect on functional connectivity they may be discernable via changes in structure-function relationship. The role of highly connected regions has also been stressed out recently. Indeed meta-analysis of graph theoretical studies has revealed that most of pathological lesions in the brain are linked to 'hubs' (Crossley et al., 2014). In the same line, recently, a "rich club" architecture has been proposed to describe the highly inter-connected core of hubs inside the brain (van den Heuvel and Sporns, 2011), which was found to be modified by pathology (Fornito et al., 2015; van den Heuvel et al., 2013). This structural core overlaps with propagation networks of epileptic activity in TLE, for example the precuneus (Arthuis et al., 2009) and as such might undergo structural and functional alterations in TLE patients, though this has yet to be demonstrated.

To our knowledge there is no study that directly evaluates the edgewise structure-function relationship at the whole brain scale, as well as within the rich-club and pathologically altered functional sub-networks in patients while taking into account network-based communication processes. In this context, we aimed to determine structure-function relationship within altered brain networks observed in rTLE. To do so we used a framework of several analytic approaches at different scales in a group of rTLE patients compared to a group of age and sex matched controls. First, structural and functional connectivity derived from dMRI/rs-fMRI data were used to examine whole brain reorganization in rTLE by using the Network Based Statistics (NBS) approach (Zalesky et al., 2010a), and by extracting the rich club structure of the brain. Second, to characterize whole brain functional-structural relationship in altered brains of rTLE patients, we sought to predict the functional connectivity from i) graph-analytical edgewise metrics derived from structural data (Goñi et al., 2014), and ii) Euclidian distance, and by comparing these results against current analytical and simulation models (Robinson et al., 2014). Third, we aimed to analyze structural-functional relationship within the altered functional subnetworks, rich-club networks and peripheral networks outside the rich club.

2. Methods

2.1. Subjects

Seven patients diagnosed with drug–resistant epilepsy of the right temporal lobe (rTLE, 4 males, mean age 31.8, range 19–50, 6 right handed, 1 left handed, for heterogeneity we selected only right lateralized patients, for detailed information see Supplementary material 1) and fourteen healthy subjects with no history of neurological disease were recruited into the study. The participants signed an informed consent form according to the rules of the local ethics committee (Comité de Protection des Personnes (CPP) Marseille 2). One control was excluded due to excessive head motion resulting in diffusion artifacts (resulting in a final control group of 13, mean age 31.8, range 20–59, 7 males, 12 right handed, 1 ambidextrous).

2.2. MRI acquisition

The participants were scanned on a Siemens Magnetom Verio 3 T MR-Scanner (Siemens, Erlangen, Germany). 350 functional MRI images were acquired in a BOLD-sensitized EPI T2*-weighted sequence with a TR of 3.6 s ($2.0 \times 2.0 \times 2.5$ mm, TE = 27 ms, 50 slices, FA = 90°), resulting in a total fMRI time series of 20 min. During the resting state protocol the subjects were asked to keep their eyes closed and not to fall asleep. The dMRI-sequence was acquired with the following parameters: angular gradient set of 64 directions, TR of 10.7 s ($2.0 \times 2.0 \times 2.0$ mm, TE = 95 ms, 70 slices, b weighting of 1000 s/mm^2). T1-weighted anatomical images were acquired with a MPRAGE-sequence (TR = 1900 ms, TE = 2.19 ms, $1.0 \times 1.0 \times 1.0$ mm, 208 slices).