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Structural covariance networks relate to the severity of epilepsy with focal-onset seizures

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ABSTRACT

Purpose: The brains of patients with epilepsy may exhibit various morphological abnormalities, which are often not directly visible on structural MR images, as they may be focally subtle or related to a more large-scale inconspicuous disorganization of brain structures. To explore the relation between structural brain organization and epilepsy characteristics, including severity and cognitive co-morbidity, we determined structural covariance networks (SCNs). SCNs represent interregional correlations of morphologic measures, for instance in terms of cortical thickness, between various large-scale distributed brain regions.

Methods: Thirty-eight patients with focal seizures of all subtypes and 21 healthy controls underwent structural MRI, neurological, and IQ assessment. Cortical thickness was derived from the structural MRIs using FreeSurfer. Subsequently, SCNs were constructed on a group-level based on correlations of the cortical thicknesses between various brain regions. Individual SCNs for the epilepsy patients were extracted by adding the respective patient to the control group prior to the SCN construction (i.e. add-one-patient approach). Calculated network measures, i.e. path length, clustering coefficient and betweenness centrality were correlated with characteristics related to the severity of epilepsy, including seizure history and age at onset of epilepsy, and cognitive performance.

Results: Stronger clustering in the individual SCN was associated with a higher number of focal to bilateral tonic-clonic seizures during life time, a younger age at onset, and lower cognitive performance. The path length of the individual SCN was not related to the severity of epilepsy or cognitive performance. Higher betweenness centrality of the left cuneus and lower betweenness centrality of the right rostral middle frontal gyrus were associated with increased drug load and younger age at onset, respectively.

Conclusions: These results indicate that the correlations between interregional variations of cortical thickness reflect disease characteristics or responses to the disease and deficits in patients with epilepsy with focal seizures.

1. Introduction

The epileptic brain often has morphological abnormalities including characteristic lesions and other subtle deviations which are not visible at radiological inspection. To understand these abnormalities, several previous studies investigated the cortical thickness in various brain regions in children and adults with epilepsy (Besseling et al. 2014; Overvliet et al. 2013; Widjaja et al. 2011). More recently, morphological brain measurements, especially cortical thickness, of various brain regions have been shown to correlate across subjects. These correlations are thought to be part of an underlying anatomical network reflecting interregional correlations of cortical thicknesses, the structural covariance network (SCN). However, whether these lesion-unspecific morphological abnormalities are related to disease characteristics of the

Abbreviations: SCN, Structural covariance network; AOP, Add one patient; LOO, Leave one out; L, Characteristic path length; C, Clustering coefficient; γ, Normalized characteristic path length; λ, Normalized clustering coefficient; TIV, Total intracranial volume

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epilepsy remains largely unknown.

The biological concept of a SCN relies on the assumption that axonally connected regions have trophic, developmental, and maturational concordances, resulting in similar variation patterns of morphology (Bernhardt et al. 2011). Since epilepsy has previously been associated with morphological changes, also distant to the seizure onset zone (Bernhardt et al. 2017; Overvliet et al. 2013), these type of group-level SCNs can be especially valuable in epilepsy studies, providing unique knowledge on interregional cortical associations (Bernhardt et al. 2013; Curwood et al. 2015; Yasuda et al. 2015). However, since the correlations between cortical thickness values of different brain regions are usually obtained by correlating the thickness values over a group of subjects, individual changes cannot be obtained directly from the group-level SCNs.

Recently, Saggar et al. presented a method for calculating individual contribution on the group-level SCN (Saggar et al. 2015). By adding one patient (AOP) to a group of healthy controls prior to the SCN construction, the individual contribution of patients on the SCN can be measured. In the current study, this individualized method will be used to obtain individual measures of the SCN.

The current study aims to assess whether there are associations between individual SCNs and characteristics related to the severity of epilepsy, including the seizure history, age at onset, drug load, and the most common comorbidity, cognitive deterioration. To our knowledge, this is the first study that relates individual SCNs based on cortical thickness to individual epilepsy characteristics.

2. Materials and Methods

2.1. Participants

We included 59 participants in this study, of which 38 were clinically diagnosed with epilepsy with focal seizures of various subtypes and 21 were healthy controls. These participants have already been investigated in a number of prior studies with different MRI modalities and study objectives (Jansen et al. 2014, 2008; Vaessen et al. 2012; Vlooswijk et al. 2011a, 2011b, 2010). All subjects gave written informed consent before participation, and had no significant clinical MR abnormalities, as assessed by a board certified neuroradiologist. Furthermore, the following epilepsy characteristics were recorded: age at onset, drug load, seizure focus (i.e. frontal, temporal, or frontotemporal and left, right or bilateral), and the number of focal seizures during lifetime. The latter was calculated using patient records and seizure diaries (Vlooswijk et al. 2011a). The lifetime number of focal seizures with and without impairment of awareness was expressed in eight categories (0, 1–10, 11–20, 21–30, 31–40, 41–50, 51–100, and > 100 seizures), since they were more likely to occur unperceived and were, therefore, less accurately reported (Vlooswijk et al. 2011a). The lifetime number of focal to bilateral tonic-clonic seizures could be extracted more accurately from the seizure diaries. Seizure focus was estimated based on EEG and seizure semiology. For all patients, no focal to bilateral tonic-clonic seizures were reported in the last two weeks before the MRI acquisition, and there were no obvious differences in the behavioral markers of patients across the different seizure foci. Drug load was calculated by using the ratio of prescribed daily dose to defined daily dose (Lammers et al. 1995). For all the participants, a full-scale IQ (FSIQ) was determined using the Wechsler Adult Intelligence Scale third edition (WAIS-III) (Wechsler 1997). A summary of the subject characteristics is provided in Table 1.

Table 1
Subject characteristics.

	Epilepsy	Controls
#Subjects	38	21
Age (in years)	40 ± 12	40 ± 14
Sex (Male/Female)	20/18	15/6
Age at onset (in years)	22 ± 13	NA
#FBTCS during lifetime	5 (21)	NA
#FSIA during lifetime	5 (7)	NA
Drug load	1.8 ± 1.1	NA
Seizure focus (F/T/FT)	14/12/12	NA
Seizure focus (L/R/Bi)	15/9/14	NA
Intelligence (FSIQ)	96 ± 15**	114 ± 15

Characteristics of patients with focal epilepsy and healthy controls. Variables are summarized as means ± standard deviations for normal data or median (interquartile range) for non-normally distributed data. FSIQ, full-scale IQ; FBTCS, focal to bilateral tonic-clonic seizures; FSIA, focal seizures with and without impairment of awareness; F, frontal; T, temporal; FT, frontotemporal; L, left; R, right; Bi, bilateral; NA, not applicable. Statistically significant differences between groups is denoted by ** $p < .01$.

2.2. MRI acquisition

Magnetic resonance imaging (MRI) was performed on a 3.0-Tesla scanner (Philips Achieva, Best, the Netherlands). T1-weighted 3D fast gradient echo images were acquired for all the participants with the following parameters: repetition time (TR) 9.91 ms, echo time (TE) 4.6 ms, inversion time (TI) 3 s, flip angle 8°, voxel size 1 × 1 × 1 mm, and matrix 256 × 256 × 200.

2.3. Analysis

2.3.1. Preprocessing

From the T1-weighted images, the cortical thickness was determined using Freesurfer (version 5.1 (Fischl et al. 2000)). The brain was parcellated into 68 cortical regions using the Desikan-Killiany atlas (Desikan et al. 2006) and the mean cortical thickness was calculated for each region.

2.3.2. Group-based SCNs

For both patients and controls, adjacency matrices were obtained by calculating the Pearson's correlation coefficient between the cortical thicknesses of each region pair. The resulting adjacency matrix elements were represented in binary values by using a threshold to select the strongest correlations. To avoid that the statistical analysis would be driven by the total number of connections (edges) in the network, the threshold was chosen such that the networks exhibit an equal number of strongest correlations, i.e. the networks are equally sparse (van Wijk et al. 2010). Negative correlations occurred fewer than 5% of the total number of correlations and were set to zero, since it is still unclear what their involvement in the network is (Gong et al. 2012). The resulting binary adjacency matrix represents the SCN, where a value of '1' denotes a connection between two regions and a '0' in the absence of a connection.

2.3.3. Individual SCNs

To extract the individual contribution of a patient on the SCN of a healthy control group, Saggar et al. introduced a so-called distance-based method (Saggar et al. 2015), in which the individual contribution of a patient can be assessed by adding one patient (AOP) to the control group before calculating the adjacency matrix. With this procedure, the SCN exhibits alterations compared to the SCN obtained from just the healthy control group, which are specific for the added patient. The SCN properties are quantified in terms of graph theoretical metrics (Fig. 1).

2.3.4. Network analysis

The SCNs are quantitatively described by two of the most robust and widely applied global graph metrics, the characteristic path length (*L*), clustering coefficient (*C*) (Watts and Strogatz 1998) as well as a regional measure, the betweenness centrality (*BC*) (Freeman 1977). *L* gives insight into how well information can spread throughout a