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## Cognitive and behavioral comorbidities in Rolandic epilepsy and their relation with default mode network's functional connectivity and organization

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### ABSTRACT

**Objective:** Rolandic epilepsy (RE) is characterized by typical interictal-electroencephalogram (EEG) patterns mainly localized in centrotemporal and parietooccipital areas. An aberrant intrinsic organization of the default mode network (DMN) due to repeated disturbances from spike-generating areas may be able to account for specific cognitive deficits and behavioral problems in RE. The aim of the present study was to investigate cognitive development (CD) and socioemotional development (SED) in patients with RE during active disease in relation to DMN connectivity and network topology.

**Methods:** In 10 children with RE and active EEG, CD was assessed using the Wechsler Intelligence Scale for Children-IV (WISC-IV); SED was assessed using the Fünf-Faktoren-Fragebogen für Kinder (FFFK), a Big-Five inventory for the assessment of personality traits in children. Functional connectivity (FC) in the DMN was determined from a 15-minute resting state functional magnetic resonance imaging (fMRI), and network properties were calculated using standard graph-theoretical measures.

**Results:** More severe deficits of verbal abilities tended to be associated with an earlier age at epilepsy onset, but were not directly related to the number of seizures and disease duration. Nonetheless, at the network level, disease duration was associated with alterations of the efficiency and centrality of parietal network nodes and midline structures. Particularly, centrality of the left inferior parietal lobe (IPL) was found to be linked with CD. Reduced centrality of the left IPL and alterations supporting a rather segregated processing within DMN's subsystems was associated with a more favorable CD. A more complicated SED was associated with high seizure frequency and long disease duration, and revealed links with a less favorable CD.

**Significance:** An impaired CD and – because of their interrelation – SED might be mediated by a common pathomechanism reflected in an aberrant organization, and thus, a potential functional deficit of the DMN. A functional segregation of (left) parietal network nodes from the DMN and a rather segregated processing mode within the DMN might have positive implications/protective value for CD in patients with RE.

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### 1. Introduction

Because of relatively mild seizures, low seizure frequency, and the typically observed spontaneous remission during adolescence, Rolandic epilepsy (RE) has been largely considered as benign focal epilepsy of childhood [1]. Recent research has come to question the benignity [2] and the largely assumed lack of sequelae [3,4] in RE.

With its typical onset between the age of 7–10 years [1], RE might critically influence the development and maturation of brain networks that are essentially involved in cognitive [4–7] and psychological [8,9] functioning. Patients with RE have been found to demonstrate specific cognitive deficits that primarily affect language and (associated) verbal abilities [10–14], visuospatial abilities [15,16], and attention [17], whereas general intellectual abilities have usually been found to be unimpaired [12,14,18]. In addition to cognitive deficits, behavioral problems are a well-documented phenomenon in RE encompassing increased levels of aggressive behavior, social and attentional problems, and elevated levels of anxiety and depression [19–21].

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Although seizures are a rare condition, RE is characterized by typical interictal-EEG patterns mainly localized in the centrotemporal (perisylvian) and parietooccipital areas [1,16,22]. The impact of focal interictal epileptic discharges (IEDs) on cognition is still a matter of debate [14,16–18,23–25]. The present literature indicates that several factors such as localization, lateralization, and focality of IEDs [14,16,23] may mediate their impact on cognitive development (CD). The findings of Nicolai et al. [24] moreover indicate that IEDs may have similar implications on cognition as seizures and might be coupled with the Concept of System Epilepsy [26].

Xiao et al. [25] found interictal epileptic activity, i.e., centrotemporal spikes (CTS) due to RE, to be associated with a brief, disrupting impact on the inferior parietal lobe (IPL) and adjacent parietal areas. The IPL constitutes a core component of the brain's default mode network (DMN) which is the most prominent resting state network of the human brain that has consistently been found to be active at rest and modulated in its activity under cognitive demands and external (task) requirements [27]. An aberrant organization of the DMN has already been related to cognitive [28,48] and psychiatric symptoms [8,9] in several pathological conditions [29]. The findings of Oser et al. [7] indicate that RE might be associated with a functional deficit within the DMN. An aberrant intrinsic organization of the DMN due to repeated disturbances that might result either from functional connectivity (FC) of spike-generating areas to DMN regions [30] and/or the involvement of core regions of the DMN (such as the IPL) in the epileptic network of RE may be, therefore, able to account for specific cognitive deficits and a more difficult CD as well as for a more complicated socioemotional development (SED) in patients with RE [25]. Thus, the aim of the present study was to investigate DMN properties, and to what extent they might be related to CD and SED in patients with RE with active interictal EEG.

## 2. Methods

### 2.1. Participants

Children with RE were recruited from the clinic for neuropediatrics and muscular diseases of the University Medical Center Freiburg. Inclusion criteria were a currently active epilepsy, as measured by interictal routine-EEG (>10 spikes/h) and sufficient compliance (and absence of contraindications) for magnetic resonance imaging (MRI).

The study was approved by the boards of Medical Ethical Committee of Freiburg University, Freiburg, Germany (Declaration of Helsinki [31]). All participants were outpatients of the Department of Neuropediatrics and Neuromuscular Diseases.

Informed written consent was gained from each participant and their parents.

### 2.2. Structural and functional data acquisition

All neuroimaging data were collected using a Siemens MAGNETOM® Prisma (Siemens, Germany), 3 Tesla MRI scanner with a 64-channel head coil at the Department for Radiology of the University Medical Center Freiburg.

Structural imaging was performed using a T1-weighted high-resolution scan (magnetization prepared acquisition gradient echo (MPRAGE)) producing 160 sagittal slices (Repetition time (TR) = 2200 ms, Echo time (TE) = 2.15 ms, field of view (FOV) 256 × 256 matrix, 1-mm isotropic voxels).

Structural imaging was followed by the acquisition of a 15-minute resting state functional magnetic resonance imaging (fMRI) using the following parameters: 3D MR-encephalography (MREG) sequence, TR = 100 ms, TE = 36 ms, 64 × 64 × 64 matrix, 3-mm isotropic voxels [32,33].

### 2.3. Data preprocessing

The MREG images were reconstructed [34] and preprocessed using the FMRIB Software Library (FSL) toolbox [35]. Preprocessing consisted of segmentation of the anatomical image to extract white matter and cerebrospinal fluid (CSF) masks, while functional images were motion-corrected and coregistered to Montreal Neurological Institute (MNI) space. Motion parameters, cardiorespiratory fluctuations [36], average white matter, and CSF time courses and polynomial drifts [37] were then regressed out of the fMRI time series at each voxel.

### 2.4. FC analysis

Functional connectivity analysis was conducted using the CONN FC toolbox v14 (<http://www.nitrc.org/projects/conn/>). Normalized structural and functional images were entered into the toolbox. Temporal correlations in the low frequency component (0.01–0.1 Hz) of the BOLD signal were computed between BOLD fluctuations in a subset of predefined regions of interest (ROIs).

### 2.5. Healthy controls

Network properties were also calculated in healthy controls, using data sets of 12 healthy children (half of them between the age of 8 and 9 years and half of them between the age of 14 and 15 years) who had participated in the Human Connectome Lifespan Project [38]. A total of 40 min of whole-brain resting-state fMRI (rfMRI) data at 3 T, with a spatial resolution of 2 × 2 × 2 mm and a temporal resolution of 720 ms was motion- and distortion-corrected using FSL toolbox [35].

Since a direct comparison of quantitative network properties between patients with RE and healthy controls from the Human Connectome Lifespan Project was not possible because of different acquisition conditions of MRI data, subsequent comparisons of network properties between the groups were performed using rank-transformed data of the subsequently calculated network measures within each subject.

### 2.6. Construction of the DMN as a functional brain network

To assess network properties, a graph-theoretical approach was used [39]. Ten ROIs consisting of medial superior frontal gyrus (med. SFG), posterior cingulate cortex (PCC), Precuneus (Prec), IPL, and angular gyrus (AG) were bilaterally extracted from the Automated Anatomical Labeling (AAL) atlas [40]. For the network construction, each ROI was taken as a node. Values of the interregional correlations served as weights of the edges between the nodes of the network resulting in a weighted symmetric FC matrix for each participant. To exclude nonsignificant connections, a threshold was set on the correlation coefficients according to a permutation test. For this purpose, surrogate data were generated by randomly shuffling the phases of the time series in the frequency domain, yielding a distribution of correlation coefficients under the null hypothesis of no connectivity. Network edges were then only preserved if their correlation coefficient exceeded a threshold corresponding to a false discovery rate (FDR) of 0.05. Topological graph-theoretical properties of the network were then calculated from the thresholded FC matrix. For the assessment of global network properties, two measures were used: global efficiency ( $E_{glob}$ ) and local efficiency ( $E_{loc}$ ). Nodal network analysis consisted of the assessment of  $E_{loc}$ , betweenness centrality (BC), and degree (K) of each node of the network.

#### 2.6.1. Neuropsychological data

Cognitive development was assessed using the German version of the Wechsler Intelligence Scale for Children (WISC-IV [41]). This test battery assesses verbal comprehension (VC), perceptual reasoning (PR), processing speed (PS), and verbal short-term span (working memory, WM). In one patient (Patient 7), solely VC and PR index scores

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