Frontal lobe connectivity and cognitive impairment in pediatric frontal lobe epilepsy

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SUMMARY

Purpose: Cognitive impairment is frequent in children with frontal lobe epilepsy (FLE), but its etiology is unknown. With functional magnetic resonance imaging (fMRI), we have explored the relationship between brain activation, functional connectivity, and cognitive functioning in a cohort of pediatric patients with FLE and healthy controls.

Methods: Thirty-two children aged 8–13 years with FLE of unknown cause and 41 healthy age-matched controls underwent neuropsychological assessment and structural and functional brain MRI. We investigated to which extent brain regions activated in response to a working memory task and assessed functional connectivity between distant brain regions. Data of patients were compared to controls, and patients were grouped as cognitively impaired or unimpaired.

Key Findings: Children with FLE showed a global decrease in functional brain connectivity compared to healthy controls, whereas brain activation patterns in children with FLE remained relatively intact. Children with FLE complicated by cognitive impairment typically showed a decrease in frontal lobe connectivity. This decreased frontal lobe connectivity comprised both connections within the frontal lobe as well as connections from the frontal lobe to the parietal lobe, temporal lobe, cerebellum, and basal ganglia.

Significance: Decreased functional frontal lobe connectivity is associated with cognitive impairment in pediatric FLE. The importance of impairment of functional integrity within the frontal lobe network, as well as its connections to distant areas, provides new insights in the etiology of the broad-range cognitive impairments in children with FLE.

KEY WORDS: All epilepsy/seizures, MRI, Functional neuroimaging, Neuropsychological assessment, All pediatric.
memory processing. Our research questions were whether fMRI activation and connectivity results differ between children with FLE compared to healthy controls, and, if so, whether these differences relate to the cognitive impairment. In addition, we investigated whether in our patient cohort clinical epilepsy characteristics could be identified that are related to fMRI changes associated with cognitive impairment.

**Methods**

**Participants**

We performed this cohort study at the Epilepsy Centre Kempenhaeghe, Heeze, The Netherlands. The Medical Ethical Committees of Kempenhaeghe and the Maastricht University Medical Centre approved this study, which is registered by the Dutch Trial Register (NTR1749).

Inclusion criteria for the patients were the following: confirmed FLE of unknown cause, age between 8 and 13 years (children above the age of 8 years were considered capable to undergo MRI scanning without sedation), no other disease that could cause cognitive decline, and no history of brain injury. All patients had a normal structural brain MRI prior to inclusion, reconfirmed by a board certified neuroradiologist. The diagnosis FLE was made when patients have had one or more clinical seizures associated with frontal focal epileptic electroencephalography (EEG) discharges. When no EEG was available during a clinical seizure, the video-recording of more than one seizure with clinical evidence of a frontal lobe origin was required to confirm the diagnosis (Provini et al., 1999). We excluded patients with frontal lobe seizures resulting from spread to the frontal lobes or with interictal epileptiform EEG abnormalities outside the frontal lobes.

Healthy age-matched controls were recruited by advertisements in local newspapers. All controls followed regular education. Exclusion criteria were medical history of head trauma or other diseases that may cause cognitive impairment.

Exclusion criteria for both groups were contraindications for MRI such as metal implants or (one of the) parents unwilling to provide informed consent.

We collected the following data for all subjects: gender, age, education level, medical history, family history, and dominant handedness.

For the patients with FLE, the following clinical epilepsy characteristics were collected via chart review: age at onset, seizure duration, seizure type, seizure frequency, seizure occurrence, history of febrile seizures, history of status epilepticus, antiepileptic drug (AED) treatment, drug load, response to AED treatment, and localization of epileptic discharges on EEG (left frontal, right frontal, or bifrontal). We computed drug load as previously described (WHO, 2008). In children using two or more AEDs, cumulative drug loads were calculated.

**Neuropsychological testing**

We performed a neuropsychological assessment of all patients prior to inclusion (see Appendix S1 for neuropsychological test details). If neuropsychological assessment had been performed within 1 year prior to inclusion, and the assessment involved all necessary tests for this study, then those test results were used. If neuropsychological assessment had been performed >1 year earlier, we repeated part of the neuropsychological assessment (see Appendix S1). The healthy control group underwent this same neuropsychological assessment.

For each participant, we evaluated test performance on three different cognitive domains to assess cognitive functioning, that is, global cognitive functioning, higher-order cognitive functioning, and fluid cognitive functioning. Global cognitive functioning reflects a trait-dependent ability. This ability shows only minor fluctuations over time (e.g., intelligence). Higher-order cognitive functioning consists of central functions that modulate and control more routine or fundamental skills (e.g., memory and verbal comprehension). Fluid cognitive functioning consists of fluctuating or state-dependent functions (e.g., attention or psychomotor speed).

Individual cognitive functioning was transformed into an impairment index, which reflects performance in the three above-mentioned cognitive domains, on a scale of 1 (severe impairment) to 8 (no impairment); see Appendix S2 for details.

Participants were grouped as cognitively impaired (i.e., an impairment index of ≤4; which means that at least global cognitive functioning is impaired) or cognitively minimal or unimpaired (impairment index ≥4).

**MRI procedure**

**Image acquisition**

MRI was performed on a 3.0-Tesla unit equipped with an 8-channel head coil (Achieva; Philips Medical Systems, Best, The Netherlands). fMRI data were acquired using a whole-brain single-shot multislice blood oxygen level-dependent (BOLD) echo-planar imaging (EPI) sequence, with repetition time (TR) 2 s, echo time (TE) 35 msec, flip angle 90 degrees, voxel size 2 × 2 × 4 mm³, 32 contiguous slices per volume, and 19 and 5 volumes per acquisition.

For anatomic reference, a T₁-weighted three-dimensional (3D) turbo field echo was acquired with the following parameters: TR 8.1 msec, TE 3.7 msec, flip angle 8 degrees, field of view (FOV) 256 × 256 × 180 mm³, and voxel size 1 × 1 × 1 mm³.

**fMRI activation task**

For the task-related fMRI we used a Sternberg letter recognition task, reflecting verbal working memory performance, to induce cerebral activation. In previous studies prefrontal and temporal areas were activated by this task.
A set of letters was visually presented to be maintained in the working memory. Subsequently, subjects responded to the presentation of single letters by pressing a button with either their right or left hand to indicate whether or not the letter was in the memorized set of letters. In the baseline condition, subjects focused on a crosshair. The task consisted of six blocks (memory set of 1–3 letters for 4 s followed by 13 response letters of 2 s each) alternated with seven baseline rest condition blocks (30 s each). The contrast between activation in baseline condition and in the loads was used for further analysis (Vlooswijk et al., 2008). Prior to the actual fMRI scanning, all study subjects successfully practiced one block inside the scanner.

Data analysis

Image preprocessing

Analysis of the time series data was performed in the Statistical Parametric Mapping (SPM8) software application (Wellcome Department of Cognitive Neurology, London, United Kingdom). Dynamic images were realigned to correct for head movements. The corrected images were coregistered with the high-resolution T1 image. The T1 image was transformed into standard Montreal Neurological Institute (MNI) space through the unified segmentation process (Ashburner & Friston, 2005). The functional images were spatially normalized by applying the transformation parameters from the unified segmentation step. Finally the functional images were spatially smoothed (8-mm Gaussian kernel).

Activation and functional connectivity analysis

Brain activation was assessed in terms of activation contrast between the task and baseline condition according to the general linear model in SPM8. A simple standard random-effects analysis was performed to assess differences in cerebral activation between the patient and control groups thresholded at the \( p < 0.05 \) level, corrected for multiple comparisons (Nichols & Holmes, 2002). First, the activation maps of the two groups were compared on a pixel-by-pixel basis and clusters of significantly (family-wise error corrected) activated brain regions were reported. Second, based on the activation maps masks were created to select the brain regions of interest. The brain regions most significantly activated were selected as regions of interest. We always included the contralateral brain region (also when not significantly activated). Time-course data were low-pass-filtered to remove the effect of high-frequency signal components and corrected for effects of head movements by using the six motion correction parameters as covariates. The temporal correlation (Pearson’s) of the filtered time series of all pairs of selected regions was calculated. The correlation coefficients between all regions were transformed into Fisher Z-values (Zar, 1996). Figure 1 demonstrates the sequence of steps between fMRI data time-series processing, connectivity matrix calculation, and statistical connectivity analysis.

Statistical analysis

Statistical data analysis was performed using the SPSS 16.0 software package (SPSS Inc., Chicago, IL, U.S.A.). Demographic and clinical characteristics were assessed using descriptive statistics. Values were expressed as mean value ± standard deviation, and between-group differences were assessed using analyses of variance (ANOVAs). To test for differences in brain activation and brain connectivity between patients and controls as well as between cognitively impaired and unimpaired patients, with general linear model, a multivariate analysis with group and gender as fixed factor and age as covariate was used. Test results were categorized by their level of statistically significance (uncorrected \( p \)-value: \( p < 0.05 \), \( p < 0.01 \), and \( p < 0.001 \)). By using a statistically significance category scheme and a plot of the connectivity matrix, a qualitative measurement of which connections and regions show an effect of interest can be made. Finally, the influence of clinical epilepsy characteristics on brain functionality was investigated. For statistical analysis, we categorized patients into short (\( \leq 5 \) years) versus long (>5 years) seizure duration, young (\( \leq 5 \) years) versus old (>5 years) age at seizure onset, low (\( \leq 1 \) seizure per week) versus high (>1 seizure per week) seizure frequency, low (\( \leq 1.0 \)) versus high (>1.0) drug load, and left versus right versus bifrontal focus, based on seizure semiology and EEG.

Figure 1.
The sequence of steps between fMRI data time-series processing, connectivity matrix calculation, and statistical connectivity analysis.

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Results

We eventually included 32 patients and 41 controls (see Appendix S3). Their demographic and clinical characteristics are recorded in Table 1.

Cognitive performance

For all included participants an impairment index could be calculated. Neuropsychological test results are recorded in Appendix S4.

Cognition was impaired in 16 children with FLE (50%) and in three healthy controls (7%). Demographic and clinical characteristics did not significantly differ between the two patient groups (see Appendix S5).

fMRI performance

All participants were able to perform the Sternberg task. Patients gave significantly fewer correct answers than controls (67 ± 10 out of 78 vs. 57 ± 21 out of 78; p < 0.001) during the Sternberg task. Cognitively impaired patients did not perform significantly worse than cognitively unimpaired patients (58 ± 21 out of 78 vs. 57 ± 20 out of 78; p = 0.849), meaning that both groups accurately performed the task. We chose relatively low cognitive loads (memory sets of 1–3 letters) in order that all participants (both 8-year-old as well as 12-year-old) could well perform the task. No differences were found between patients and healthy controls and between cognitively impaired and unimpaired patients for the different cognitive loads. This does not exclude that higher cognitive loads could indeed have made a difference between patients and controls (Vollmar et al., 2011; Stretton et al., 2012).

Sternberg activation maps

Quantitatively, patients showed lower cerebral activation in several regions during the Sternberg task compared to controls (see Fig. 2). However, after correction for multiple comparisons (family wise error, SPM), this difference proved statistically not significant.

The brain regions most significantly activated during Sternberg task performance and their contralateral counterparts were selected as regions of interest. The 27 selected brain regions for further analysis included the anterior cingulate cortex, bilateral middle frontal gyrus, bilateral frontal pole, bilateral precentral gyrus, bilateral superior parietal lobe, bilateral supramarginal gyrus, bilateral superior temporal gyrus, bilateral middle temporal gyrus, bilateral lateral occipital cortex, bilateral hippocampus, bilateral thalamus, bilateral pallidum, brainstem, and cerebellum.

Functional connectivity

All the 351 unique connections between these 27 selected areas ((27 × 26)/2) were used for brain connectivity analysis. Results of the between-group analysis of pair-wise connection strength were all corrected for gender and age. The results did not differ if the three cognitively impaired controls were excluded.

Patients showed significantly less functional connectivity than controls, between areas throughout the entire brain (see the connectivity matrix in Fig. 3A). The right superior parietal lobe, right and left thalamus, anterior cingulate cortex, as well as right hippocampus were the brain areas with least functional connectivity.

Table 1. Demographic and clinical characteristics of the (A) control and (B) epilepsy groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>19:22</td>
</tr>
<tr>
<td>Age</td>
<td>10.5 ± 1.5 years</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>18:14</td>
</tr>
<tr>
<td>Age</td>
<td>11.3 ± 1.3 years</td>
</tr>
<tr>
<td>Mean age (±SD) at seizure onset</td>
<td>4.9 ± 2.8 years</td>
</tr>
<tr>
<td>Mean duration (±SD) of epilepsy</td>
<td>6.1 ± 2.8 years</td>
</tr>
<tr>
<td>Seizure type</td>
<td></td>
</tr>
<tr>
<td>Complex partial seizures only</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Atypical absence seizures only</td>
<td>13 (41)</td>
</tr>
<tr>
<td>Atypical absences and other complex partial seizures</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Secondary generalized tonic–clonic seizures</td>
<td>5 (15)</td>
</tr>
<tr>
<td>History</td>
<td></td>
</tr>
<tr>
<td>Febrile seizures</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Seizure occurrence</td>
<td></td>
</tr>
<tr>
<td>Seizure-free</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Nocturnal seizures only</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Diurnal seizures only</td>
<td>12 (38)</td>
</tr>
<tr>
<td>Both nocturnal and diurnal seizures</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Seizure frequency (in the past year)</td>
<td></td>
</tr>
<tr>
<td>Low seizure frequency (&lt;1 seizure/month)</td>
<td>13 (41)</td>
</tr>
<tr>
<td>High seizure frequency (&gt;1 seizure/month)</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Refractory</td>
<td>21 (66)</td>
</tr>
<tr>
<td>Not refractory</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Seizure focus based on history and EEG</td>
<td></td>
</tr>
<tr>
<td>Focus left frontal</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Focus right frontal</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Focus bifrontal</td>
<td>17 (53)</td>
</tr>
<tr>
<td>AED treatment</td>
<td></td>
</tr>
<tr>
<td>No AED</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>21 (66)</td>
</tr>
<tr>
<td>Polytherapy</td>
<td>10 (31)</td>
</tr>
<tr>
<td>Drug load</td>
<td></td>
</tr>
<tr>
<td>Low &lt;1.0</td>
<td>26 (81)</td>
</tr>
<tr>
<td>High ≥1.0</td>
<td>6 (19)</td>
</tr>
</tbody>
</table>

EEG, electroencephalography; AED, antiepileptic drug; SD standard deviation.
Cognitively unimpaired patients demonstrated significantly less functional connectivity than controls, between areas throughout the whole brain, specifically in the right and left thalamus, right middle frontal gyrus, and right superior parietal lobe (Fig. 3B). In addition, cognitively impaired patients showed significantly less functional connectivity than controls, again between areas throughout the whole brain, although especially in the left precentral gyrus, right superior parietal lobe, right thalamus, and anterior cingulate cortex (Fig. 3C).

Comparison of the cognitively impaired with unimpaired patients revealed a subset of 14 connections that showed significantly less functional connectivity. Remarkably, these connections encompassed frontal lobe connections only. These were not only connections between different frontal lobe areas, but also between the frontal lobe and distant brain areas, that is, the parietal lobe, temporal lobe, basal ganglia, and cerebellum (see Table 2 and Fig. 4).

**Influence of clinical epilepsy characteristics**

The connection strengths of the 14 specific frontal lobe connections, which demonstrated decreased functional connectivity in cognitive impaired patients compared to cognitively unimpaired patients, were not associated with any of the clinical epilepsy characteristics, including age at seizure onset, duration of epilepsy, seizure occurrence, seizure frequency, side of seizure focus, history of febrile seizures or status epilepticus, use of monotherapy versus polytherapy, or drug load (p > 0.05).

For 2 of these 14 connections, we found an association between seizure type and functional connectivity. The connectivity between the right precentral gyrus and right superior parietal lobe (p = 0.030) as well as the right precentral gyrus and right supramarginal gyrus (p = 0.029) was less in patients with frontal absences and other complex partial seizures compared to patients with other seizure types.

**Discussion**

**Current findings**

Children with FLE displayed a widespread decrease in functional brain connectivity compared to controls during working memory task performance, whereas the mean activation pattern remained relatively similar. The widespread decrease in functional brain connectivity was similar in the cognitively impaired and unimpaired patients, which suggests that it is related to the epilepsy itself, irrespective of patients’ cognitive performance. Alternatively, a common underlying cause could lead to both functional brain disturbances as well as to epilepsy.

**Link to cognitive impairment**

 Patients with cognitive impairment showed decreased functional connectivity in a specific subset of connections. In line with our expectations, this subset encompasses only frontal lobe connections. These do not only connect different frontal lobe areas, but also connect the frontal lobe with distant brain areas, that is, the parietal lobe, temporal lobe, basal ganglia and cerebellum. This may explain the broad range of cognitive domains—including typical frontal lobe functions as well as extrafrontal functions—that reveal deficits in children with FLE of unknown cause (Braakman et al., 2011, 2012). This broad range of cognitive impairment is not specific for FLE only; in patients with temporal lobe epilepsy (TLE), impairments of typical temporal lobe functions such as memory are observed alongside deficits of typical frontal lobe functions, such as executive functions (Strettton & Thompson, 2012). In TLE, decreased functional connectivity may also affect connections within the temporal lobes as well as to distant areas.

This is the first study that relates fMRI results to cognitive functioning in children with epilepsy. The fact that FLE and its complications become apparent in childhood stresses the
importance of studying this etiology in children (Braakman et al., 2011).

Results of previous fMRI studies in adult patients with epilepsy

The few studies that have related fMRI results to cognitive functioning have been performed in adults with TLE, not FLE. fMRI studies in adult patients with TLE revealed that memory impairment was associated with shifts of brain activation to the hemisphere contralateral to the seizure focus (Powell et al., 2007; Vannest et al., 2008; Wagner et al., 2008), or to other areas that did not show activation in controls during memory tasks (Dupont et al., 2000). A decrease in activation in the inferior frontal area in TLE patients was associated with better language task performance, whereas patients with normal or increased activation patterns performed worse (Weber et al., 2006). Other studies did not find differences in brain activation patterns between cognitively impaired patients with epilepsy and controls. In an fMRI study performed in patients with juvenile myoclonic epilepsy, activation pattern in patients with impaired working memory performance did not differ from healthy controls (Roebling et al., 2009). Moreover, patients with cryptogenic localization-related epilepsy complicated by language impairment did not show a different activation pattern during language task performance compared to controls (Vlooswijk et al., 2010).
Similar to the findings in the current study, functional connectivity studies in adult patients with mesial TLE have shown that altered connectivity (i.e., either decreased or increased) is observed not only in the network of mesiotemporal structures, that is, structures in which the seizure focus resides (Bettus et al., 2009), but also in network structures distant from the seizure focus (Waites et al., 2006; Voets et al., 2009; Liao et al., 2010; Zhang et al., 2010; Luo et al., 2011). The exact relation between these altered functional networks and cognition in epilepsy remains to be elucidated. Decreased functional connectivity may reflect diminished function of a structure in the network; for example, the impaired language performance in patients with cryptogenic localization-related epilepsy was associated with decreased connectivity in the language networks (Vlooswijk et al., 2010). Increased functional connectivity may reflect enhanced function owing to compensatory mechanisms; increased functional connectivity between the anterior and posterior hippocampus contralateral to the seizure focus was correlated with better working memory performance in patients with TLE (Bettus et al., 2009).

Methodologic consideration on many connections

When connection strengths between multiple brain regions are compared, results should be discussed in regard to the likelihood of encountering false positives. Standard multiple comparisons correction methods such as Bonferroni correction (Holm, 1979) or false discovery rate control (Benjamini & Hochberg, 1995) are not tailored for application in connectivity analysis and might be too stringent.

The defined 27 regions of interest have 351 connections. Nine of these 27 brain regions (1 of 3) were frontal lobe regions (i.e., anterior cingulate cortex, bilateral middle frontal gyrus, bilateral precentral gyrus, and bilateral insula). This means that we consider 198 (56%) possible frontal lobe and 153 (44%) nonfrontal lobe connections. When the control for finding false positives is set to 5% (p = 0.05), we expect to encounter 18 false-positive connection-strength differences for the comparison between patients and controls. This set of false positives would equally distribute over the entire set of defined connections; thus would appear approximately as 10 frontal lobe and 8 nonfrontal lobe connection differences. One could argue

### Table 2. The subset of frontal lobe connections that showed significantly less functional connectivity in the cognitively impaired patients than in the cognitively unimpaired patients

<table>
<thead>
<tr>
<th>Connections between different brain regions</th>
<th>Signal change in cognitively unimpaired patients, mean ± SD</th>
<th>Signal change in cognitively impaired patients, mean ± SD</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate cortex–left superior parietal lobe</td>
<td>0.70 ± 0.30</td>
<td>0.44 ± 0.31</td>
<td>0.017</td>
</tr>
<tr>
<td>Right insula–right frontal pole</td>
<td>0.78 ± 0.24</td>
<td>0.44 ± 0.38</td>
<td>0.009</td>
</tr>
<tr>
<td>Left precentral gyrus–right superior parietal lobe</td>
<td>0.48 ± 0.45</td>
<td>0.30 ± 0.33</td>
<td>0.035</td>
</tr>
<tr>
<td>Left precentral gyrus–right middle temporal gyrus</td>
<td>0.59 ± 0.32</td>
<td>0.37 ± 0.28</td>
<td>0.048</td>
</tr>
<tr>
<td>Left precentral gyrus–right superior temporal gyrus</td>
<td>0.46 ± 0.36</td>
<td>0.26 ± 0.26</td>
<td>0.026</td>
</tr>
<tr>
<td>Left precentral gyrus–right hippocampus</td>
<td>0.38 ± 0.35</td>
<td>0.15 ± 0.35</td>
<td>0.042</td>
</tr>
<tr>
<td>Left precentral gyrus–left pallidum</td>
<td>0.43 ± 0.32</td>
<td>0.16 ± 0.27</td>
<td>0.021</td>
</tr>
<tr>
<td>Left precentral gyrus–right pallidum</td>
<td>0.35 ± 0.35</td>
<td>0.17 ± 0.32</td>
<td>0.016</td>
</tr>
<tr>
<td>Left precentral gyrus–left frontal pole</td>
<td>0.40 ± 0.25</td>
<td>0.28 ± 0.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Right precentral gyrus–right superior parietal lobe</td>
<td>0.58 ± 0.30</td>
<td>0.32 ± 0.37</td>
<td>0.004</td>
</tr>
<tr>
<td>Right precentral gyrus–cerebellum</td>
<td>0.46 ± 0.24</td>
<td>0.25 ± 0.40</td>
<td>0.045</td>
</tr>
<tr>
<td>Right precentral gyrus–right supramarginal gyrus</td>
<td>0.83 ± 0.37</td>
<td>0.47 ± 0.26</td>
<td>0.004</td>
</tr>
<tr>
<td>Left superior parietal lobe–right frontal pole</td>
<td>0.58 ± 0.37</td>
<td>0.36 ± 0.37</td>
<td>0.015</td>
</tr>
<tr>
<td>Left superior temporal gyrus–right frontal pole</td>
<td>0.53 ± 0.24</td>
<td>0.36 ± 0.22</td>
<td>0.025</td>
</tr>
</tbody>
</table>

SD, standard deviation.

**Figure 4.**

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that the observed 14 connectivity abnormalities cannot be discerned from the expected number of false positives. Nonetheless, the 14 connections with decreased connectivity we found in the current study are all frontal lobe connections. This observation is unlikely to result from false positives alone. Actually, the chance of finding 14 abnormal frontal and zero nonfrontal connections is equal to $p = (0.56)^{14}(1−0.56)^{14} = 0.0003$. Therefore, we argue that the observation of multiple decreased frontal connections sustains the multiple comparison problem. However, the results should be interpreted with caution given the limitations of partially correcting for multiple comparisons. The recent work by Zalesky et al. (2010) could possibly infer on the significance of individual connections by using a network based statistics method.

### Conclusion

Patients with FLE complicated by cognitive impairment showed decreased functional connectivity in a specific subset of frontal lobe connections. These include connections between different frontal lobe areas, as well as connections to distant brain areas. The importance of the loss of functional integrity within the frontal lobe network, as well as in its connections to distant areas provides new insights in the etiology of the broad-range cognitive impairments in children with FLE. Clinical epilepsy characteristics appear to have limited influence on the integrity of this frontal lobe network.

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### Disclosures

The authors have no conflicts of interest. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

### References


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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

- **Appendix S1.** Neuropsychological test details.
- **Appendix S2.** Impairment index composition details.
- **Appendix S3.** Flowchart of inclusion.
- **Appendix S4.** Neuropsychological test results.
- **Appendix S5.** Demographic and clinical characteristics of the epilepsy group.