Memory processes and prefrontal network dysfunction in cryptogenic epilepsy


SUMMARY

Purpose: Impaired memory performance is the most frequently reported cognitive problem in patients with chronic epilepsy. To examine memory deficits many studies have focused on the role of the mesiotemporal lobe, mostly with hippocampal abnormalities. However, the role of the prefrontal brain remains unresolved. To investigate the neuronal correlates of working memory dysfunction in patients without structural lesions, a combined study of neurocognitive assessment, hippocampal and cerebral volumetry, and functional magnetic resonance imaging of temporal and frontal memory networks was performed.

Methods: Thirty-six patients with cryptogenic localization-related epilepsy and 21 healthy controls underwent neuropsychological assessment of intelligence (IQ) and memory. On T1-weighted images obtained by 3-Tesla magnetic resonance imaging (MRI), volumetry of the hippocampi and the cerebrum was performed. Functional MRI (fMRI) was performed with a novel picture encoding and Sternberg paradigm that activated different memory-mediating brain regions. Functional connectivity analysis comprised cross-correlation of signal time-series of the most strongly activated regions involved in working memory function.

Key Findings: Patients with epilepsy displayed lower IQ values; impaired transient aspects of information processing, as indicated by lower scores on the digit-symbol substitution test (DSST); and decreased short-term memory performance relative to healthy controls, as measured with the Wechsler Adult Intelligence Scale subtests for working memory, and word and figure recognition. This could not be related to any hippocampal volume changes. No group differences were found regarding volumetry or fMRI–derived functional activation. In the Sternberg paradigm, a network involving the anterior cingulate and the middle and inferior frontal gyrus was activated. A reduced strength of four connections in this prefrontal network was associated with the DSST and word recognition performance in the patient group.

Significance: Deficits in the processes involved in transient working memory, and to a lesser extent in short-term memory, in patients with localization-related epilepsy of both temporal and extratemporal origin can not be attributed to hippocampal atrophy or function only, but are also related to reduced functional connectivity in the prefrontal brain. Because patients with symptomatic lesions or mesiotemporal sclerosis were excluded from this study, the results cannot be explained by structural lesions. Therefore, the current findings highlight the influence of epilepsy on the prefrontal network integrity as a possible underlying problem of memory impairment.

KEY WORDS: Epilepsy, Functional neuroimaging, Memory, Volumetry, Prefrontal network.

Patients with chronic epilepsy commonly develop comorbid cognitive problems, ranging from memory deficits and mental slowing, to global cognitive deterioration (Oyegbile et al., 2004). Several aspects of memory can be disturbed, including verbal and figural encoding, working memory, and long-term memory (Helmstaedter, 2002).

Different clinical factors contribute to cognitive impairment in epilepsy, such as antiepileptic drugs (AEDs) (Jokeit et al., 2005), interictal epileptic discharges (Aldenkamp & Arends, 2004), and severity of seizures (Dodrill, 2002; Thompson & Duncan, 2005). However, the impact on cognition of these factors can be highly variable. A comprehensible model for the development of memory impairment in epilepsy is still lacking.
A more rewarding approach may be the investigation of cerebral mechanisms that could be responsible for memory dysfunction. Such mechanisms may be the mediator between epilepsy factors and the development of memory impairment. Usually, this is studied by attempting to find an association with macrostructural abnormalities on magnetic resonance imaging (MRI), for example, by focusing on hippocampal sclerosis and atrophy, as these are related to memory impairment. Studies using functional MRI (fMRI) are often integrated in the workup procedure for epilepsy surgery and focused on patients with medically refractory temporal lobe epilepsy (TLE), generally with unilateral hippocampal or mesiotemporal abnormalities (Crane & Milner, 2005; Baxendale et al., 2008; Binder et al., 2008; Powell et al., 2008; Cheung et al., 2009).

In clinical practice though, memory problems are reported not only by patients with unilateral TLE, but also by those with extratemporal lobe epilepsy and by patients without any structural lesions. These observations suggest that (1) dysfunction of structures outside the mesiotemporal lobe may cause memory deficits and (2) memory problems are not solely attributable to structural cerebral lesions.

Based on the “model of working memory” proposed by Baddeley & Hitch (1974), the term working memory covers the very early, transient aspects of information processing. Central components of the working memory model are the “central executive,” referring to the supervisory system that controls the flow of information from and to its slave systems: the “phonological loop” (a transient verbal storage system), the “visuospatial sketchpad” (transient visuo-spatial storage system), and the “episodic buffer” (which links the working memory to more stable phases of the short-term memory system) (Fig. 1). Theoretically, the cerebral regions involved in the central executive function, may well be located outside the temporal lobe, most likely in the prefrontal regions. Impairment of the central executive can lead to deficits in short-term memory as well.

Conventional MRI is not suited for detection of early changes associated with cognitive decline. However, with newer MR techniques, more subtle cerebral changes can be investigated. With fMRI, for instance, functional activation patterns during a cognitive task can be localized. Most fMRI studies describe group differences in activation patterns in homogeneous populations with TLE. A disruption of the memory network, independently of whether the temporal or extratemporal nodes in this network are dysfunctional, might result in the same types of memory impairment. With functional connectivity analysis, the integrity of such networks can be investigated.

The aim of the study was to investigate memory performance in patients with cryptogenic epilepsy of both temporal and extratemporal origin as compared to controls, and to explore the relation with brain volume and function. To assess brain function, we have investigated the relation of memory performance and functional connectivity in the hippocampus and the prefrontal networks. This exploration might reveal a possible etiologic explanation for the development of memory deficits in patients with cryptogenic localization-related epilepsy.

**Methods**

**Participants**

Patients with cryptogenic temporal or extratemporal localization-related epilepsy were recruited from the Epilepsy Centre Kempenhaeghe (Heeze, The Netherlands) and the outpatient Neurology Department of the Maastricht University Medical Centre. Cryptogenic was defined by the absence of structural abnormalities on previous imaging (1.5-Tesla MRI) and exclusion of other causes. Other inclusion criteria were no history of status epilepticus or other underlying disease that potentially causes cognitive impairment. Healthy controls were family members and acquaintances of the patients without a history of brain injury or cognitive problems.

After careful selection (see Fig. 2), the study population included 36 patients (19 women; mean age 39 years) and 21 healthy controls (12 women; mean age 40 years). All subjects gave written informed consent, and approval for the study by the local medical ethical commission was obtained.

The following patient data were collected: age at onset of epilepsy, seizure focus, drug load, and total number of partial and secondarily generalized seizures (SGS) during lifetime. The latter was calculated using patient records and seizure diaries. Because partial seizures are more prone to occur unperceived and, therefore, less accurately reported, the estimation of partial seizures is expressed in categories.

Drug load was calculated by using the ratio of prescribed daily dose to defined daily dose (Lammers et al., 1995). Characteristics of patients and controls are listed in Table S1 of the Supporting Information.

**Neurocognitive testing**

All subjects underwent assessment of intelligence and memory. The selection of memory tests was based on assessing those functions that could also be evaluated during
fMRI, focusing on working memory and encoding (as necessary for episodic memory). To test intelligence, the Wechsler Adult Intelligence Scale (WAIS-III) was used (Wechsler, 1997) with administration of all subtests in the majority of patients. As a measure for the central executive, involved in the early transient memory processes, the WAIS-III subtest digit-symbol substitution test (DSST) was used (Byrne, 1998; Pukrop et al., 2003). For the more stable components of working memory, we used the normalized scores from the WAIS-III subtests included in the Working Memory Index: digit span, letter-number sequencing, and arithmetic. Furthermore, two recognition tasks for words and figures from the FePsy test (Alpherts & Aldenkamp, 1994) were administered. Handedness was assessed with the Annett Handedness Questionnaire (Annett, 1970). Based on the performance on the DSST (<9) and the word recognition task (<18), two separate groups of cognitively impaired patients were defined. The former consists of 19 impaired patients (vs. 17 unimpaired) and the latter of 12 impaired patients (vs. 24 unimpaired).

fMRI data acquisition

MRI was performed on a 3-Tesla unit (Philips Achieva, Best, The Netherlands), equipped with an 8-channel head coil. fMRI data were acquired using a whole-brain blood oxygen level-dependent (BOLD) echo-planar imaging sequence, with repetition time 2 s (3 s for picture encoding), echo time 35 ms, matrix 128 × 128 × 32, field of view (FOV) 256 × 256 mm², 4 mm adjacent transverse slices, and 196 volumes per acquisition. For anatomic reference, a T₁-weighted three-dimensional (3D) turbo field echo was acquired with the following parameters: TR 9.91 ms, TE 4.6 ms, inversion time 3 s, flip angle 8 degrees, voxel size 1 × 1 × 1 mm³, matrix 256 × 256 × 200, 1 mm coronal slices.

fMRI activation paradigms

Two fMRI activation paradigms were selected to investigate different memory networks: picture encoding for activation of the hippocampus and surrounding areas and Sternberg for activation of the prefrontal network. For a detailed description of these paradigms, see the Supporting Information – Appendix S1.

Image analysis

fMRI data analysis was performed in MATLAB (Mathworks, Natick, MA, U.S.A.) using brain activation contrasts (between task performance and baseline) according to the General Linear Model (GLM) as implemented in the statistical parametric mapping software package (SPM2) (Wellcome Department of Cognitive Neurology, London, United Kingdom). The BOLD images were realigned, transformed into the standardized Montreal Neurological Institute (MNI) space, and smoothed with a 6-mm Gaussian kernel. In the GLM, the standard discrete cosine-set was used to correct for (low-frequency) nuisance. In addition, the time-series were convolved with the hemodynamic response function.

A standard random-effects analysis was performed to explore differences between the epilepsy and control group. Results were thresholded at the p < 0.05 level (corrected for multiple comparisons). In addition, connectivity analysis was performed using SPM2. Based on the activation maps of the control group, and the anatomic regions identified in the template MNI image, standard masks were created to select the regions of interest activated in the picture encoding and Sternberg paradigms. For the hippocampus, individual masks were manually drawn for the volumetric analysis. The regions included were hippocampi (HC), lingual gyrus (LG), and anterior cingulate cortex (ACC) for the picture encoding paradigm, and bilateral inferior frontal gyrus (IFG), bilateral middle frontal gyrus (MFG), and ACC for the Sternberg paradigm. The signal change between activation and rest was averaged yielding an average individual BOLD response during both tasks within that region (Riecker et al., 2003).

For the connectivity analysis, an fMRI signal vector from the regions of interest with the course of signal intensity over the 196 volumes was obtained for every subject (Waites et al., 2006). Each vector was low-pass-filtered to remove the effect of high-frequency noise. The six motion correction parameters were included as confounders. The correlation coefficients of all signal intensities vectors for all regions were calculated, and transformed using the Fisher-Z transformation. Finally, for the possible connections (6 for picture encoding; 10 for Sternberg), a mean
connectivity Z-value was obtained to compare with neurocognitive, volumetric, and epilepsy parameters.

**Volumetry**

For all subjects, the hippocampi were manually outlined using the freeware software program MRICron (Rorden, 2007) by two observers who were blinded to all subject information. The delineation protocol, the hippocampal boundaries, and the correction for brain volume are described in detail elsewhere (Jeukens et al., 2009). Hippocampal volumes were calculated by multiplying the number of voxels by the voxel volume (1 mm³). The final volume of the hippocampus was determined as the mean of volumes delineated by the two observers. Brain volume was determined by automated segmentation in SPM2, and comprised the total white and gray matter tissue volume of the cerebrum.

**Statistical analysis**

Clinical, neuropsychological, and volumetric data analyses were performed in SPSS (Rel. 16.0.1; SPSS Inc., Chicago, IL, USA). To acquire a standardized mean connectivity value for both fMRI paradigms, z-scores for all connections were calculated and averaged. Functional connectivity values, including the z-scores for mean functional connectivity, were compared with the neuropsychological test scores, age at onset, and drug load using Pearson correlation. For correlation with seizure frequency, Spearman correlation was performed. In addition, possible differences between patients with epilepsy and healthy volunteers were assessed using a Student’s t-test. Post hoc analysis included one-way analysis of variance (ANOVA) assessing possible differences associated with seizure focus (frontal, frontotemporal, temporal focus and healthy volunteers).

### RESULTS

**Neurocognitive performance**

The patient group as a whole had lower IQ scores than controls, as well as worse performance on all other neuropsychological tests. The results of the included patients were overall in the average range, but there was a broad range of cognitive performance, with a subset of patients with evident cognitive impairment. On the contrary, the range of cognitive test results is limited in the control group, with most subjects performing at or around the average group value (Table 1).

**Hippocampal and brain volumetry**

The left hippocampus was on average 3–6% smaller than the right hippocampus in both groups (patients p < 0.01, controls p = 0.02). When comparing patients with controls, it was noted that hippocampal volumes were slightly smaller for the patient group, but these differences were not significant (p = 0.07 left hippocampus; p = 0.17 right hippocampus) and were comparable to the interobserver variation [±7% (Jeukens et al., 2009)]. Subgroup analysis according to seizure focus did not reveal left-right differences for hippocampal volumes. No correlation between hippocampal volumes or brain volume and neuropsychological test results was found (Table 2).

**fMRI: performance**

Both groups performed well on the fMRI paradigms, as measured by monitoring of the button presses during fMRI. Only on the Sternberg paradigm, patients exhibited significantly longer reaction times than controls (822 ± 164 ms for patients vs. 699 ± 77 ms for controls, p < 0.01). Reaction times during picture encoding and error rates on both paradigms were comparable in both groups. These results confirm that both groups could perform the paradigms adequately, and that fMRI results can be interpreted reliably.

**fMRI: picture encoding paradigm**

**Activation maps and functional connectivity**

Significant activation was seen bilaterally in the mesiotemporal, anterior cingulate, visual and visual association cortex, and left thalamus (Fig. 3D, E). No significant differences were found between patients and controls for either activation maps or functional connectivity values (Fig. 3F, Table 3).

**Correlation of functional connectivity values with neurocognitive memory performance**

did not reveal any significant results.

**fMRI: Sternberg paradigm**

**Activation maps and functional connectivity**

Significant activation was seen bilaterally in the inferior frontal gyrus, middle frontal gyrus, anterior cingulate, visual association cortex, and cerebellum (Fig. 3A, B). No significant differences were found in activation maps or functional connectivity values between patients and controls (Fig. 3C, Table 3).

**Correlation of connectivity values with neurocognitive memory performance**

demonstrated a significant correlation between the digit-symbol substitution test and 4 of the 10

---

**Table 1. Neuropsychological test results of patients and healthy controls**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients (±SD)</th>
<th>Range</th>
<th>Healthy controls (±SD)</th>
<th>Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-scale IQ</td>
<td>96 ± 16</td>
<td>61–129</td>
<td>114 ± 16</td>
<td>88–147</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Digit-symbol substitution test</td>
<td>9 ± 4</td>
<td>2–17</td>
<td>12 ± 3</td>
<td>7–18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Letter-number sequencing</td>
<td>10 ± 4</td>
<td>2–19</td>
<td>12 ± 3</td>
<td>8–18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Digit span</td>
<td>10 ± 4</td>
<td>4–17</td>
<td>12 ± 2</td>
<td>7–16</td>
<td>0.02</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>10 ± 3</td>
<td>4–18</td>
<td>12 ± 3</td>
<td>8–17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Word recognition</td>
<td>19 ± 3</td>
<td>7–23</td>
<td>21 ± 2</td>
<td>18–24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Figure recognition</td>
<td>12 ± 4</td>
<td>3–22</td>
<td>14 ± 4</td>
<td>8–20</td>
<td>0.02</td>
</tr>
</tbody>
</table>
studied connections in the patient group, that is, ACC-right MFG ($r = 0.34$, $p = 0.04$), right MFG-left MFG ($r = 0.41$, $p = 0.01$), right MFG-left IFG ($r = 0.38$, $p = 0.02$), and left IFG-right IFG ($r = 0.35$, $p = 0.04$) (Fig. 4A). The impaired patient group (based on DSST scores) displayed significantly lower connections than nonimpaired patients for these four connections ($p < 0.036$).

For two of these connections a significant correlation was demonstrated with the results of the word recognition test (ACC-right MFG, $r = 0.35$, $p = 0.04$; and right MFG-

Table 2. Hippocampal and intracranial volumes (in cm$^3$) for patients and healthy controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Left HC ± SD</th>
<th>Right HC ± SD</th>
<th>ICV ± SD</th>
<th>Left HC$_{corr}$ ± SD</th>
<th>Right HC$_{corr}$ ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients versus controls</td>
<td>2.965 ± 0.430</td>
<td>3.141 ± 0.392</td>
<td>1252 ± 146</td>
<td>3.007 ± 0.357</td>
<td>3.182 ± 0.357</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>3.182 ± 0.405</td>
<td>3.294 ± 0.405</td>
<td>1272 ± 128</td>
<td>3.182 ± 0.358</td>
<td>3.294 ± 0.326</td>
</tr>
<tr>
<td>p-value</td>
<td>0.07</td>
<td>0.17</td>
<td>0.46</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>Patients divided according to side of seizure focus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided</td>
<td>3.025 ± 0.569</td>
<td>3.146 ± 0.492</td>
<td>1286 ± 128</td>
<td>2.996 ± 0.497</td>
<td>3.117 ± 0.468</td>
</tr>
<tr>
<td>Right-sided</td>
<td>2.891 ± 0.410</td>
<td>3.086 ± 0.359</td>
<td>1173 ± 131</td>
<td>3.089 ± 0.237</td>
<td>3.284 ± 0.195</td>
</tr>
<tr>
<td>Bilateral</td>
<td>2.967 ± 0.367</td>
<td>3.163 ± 0.365</td>
<td>1267 ± 155</td>
<td>2.977 ± 0.324</td>
<td>3.174 ± 0.351</td>
</tr>
</tbody>
</table>

HC, hippocampus; SD, standard deviation; ICV, total intracranial volume; HC$_{corr}$, hippocampal volume corrected for total intracranial volume.

No significant differences between groups based on side of seizure focus, calculated with one-way ANOVA.

Figure 3.

Group averaged fMRI activation maps superimposed on a normalized T1-weighted MR image. Mean activation patterns for patients are shown in A and D and for healthy controls in B and E. For the Sternberg paradigm the characteristic bilateral prefrontal network is shown on coronal slices (A–C). For the picture encoding paradigm (D–F) the characteristic activation clusters in the hippocampi and visual association cortex are shown on coronal (D1 and E1) and sagittal (D2 and E2) slices. The selected regions of interest with the functional connectivity values for patients (in black) and controls (in white) for all the connections between these regions are schematically illustrated in a coronal (C) and transverse (F) slice. Connection strengths were not significantly different between the two groups ($p > 0.05$). Locations of the structures on the schematic illustration are not accurate and are positioned for reasons of clarity. The color bar indicates the t-value of the activation level. Slice positions are specified in the MNI coordinate system: $y = 16$ mm for A and B; $y = -20$ mm for D1 and E1; $x = 22$ mm for D2 and E2. ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; HC, hippocampus; l, left; r, right; LG, lingual gyrus.

Epilepsia © ILAE
MFG, $r = 0.34, p = 0.04$). The connection ACC-left MFG demonstrated a trend toward significant correlation with the word recognition test ($r = 0.29, p = 0.08$) (Fig. 4B). The impaired patient group (based on word recognition scores) displayed significantly lower connections than nonimpaired patients for these four connections complemented with the left IFG-right IFG and left IFG-right MFG connections ($p < 0.013$).

In the healthy control group, 4 of 10 connections (ACC-left IFG ($r = 0.49, p = 0.02$), ACC-right IFG ($r = 0.44, p = 0.04$), ACC-right MFG ($r = 0.45, p = 0.04$), left IFG-right MFG ($r = 0.44, p = 0.05$), as well as the Z-score for mean functional connectivity ($r = 0.45, p = 0.04$) were associated with performance on arithmetic. For the other neuropsychological memory tests, no correlations with functional connectivity were found in the healthy controls.

**Clinical parameters**

In the Sternberg paradigm, higher age at onset was correlated with lower functional connectivity for ACC–right MFG ($r = -0.34, p = 0.04$). For the connection right IFG–left MFG, higher values were correlated with higher drug load ($r = 0.42, p = 0.01$). No other clinical parameters (age, lifetime number of seizures, drug load, side or site of seizure focus) correlated with the fMRI results.

**Discussion**

**Current findings**

In this study, memory impairment in patients with cryptogenic epilepsy was studied by neurocognitive assessment, volumetry, and fMRI. Compared to controls, patients performed worse on all memory tests. Neuropsychological test results of patients ranged from evidently disturbed to normal, with some overlap with results from healthy controls. The memory impairment observed could not convincingly be related to smaller hippocampal or brain volumes. In addition, no significant overall group differences could be demonstrated for functional activation maps or functional connectivity values. Focusing on the patients only, lower functional connectivity values for 4 of 10 possible connections between the activated regions in the Sternberg paradigm was associated with worse performance on the digit-symbol substitution test. This suggests that especially the central executive component of working memory is susceptible for the influence of epilepsy. Moreover, some of

---

**Table 3. Functional activation levels (percentage signal change ± SD)**

<table>
<thead>
<tr>
<th>ROIs</th>
<th>Patients</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Picture encoding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>0.30 ± 0.14</td>
<td>0.30 ± 0.18</td>
</tr>
<tr>
<td>Left HC</td>
<td>0.43 ± 0.19</td>
<td>0.52 ± 0.19</td>
</tr>
<tr>
<td>Right HC</td>
<td>0.46 ± 0.18</td>
<td>0.54 ± 0.20</td>
</tr>
<tr>
<td>LG</td>
<td>0.43 ± 0.25</td>
<td>0.59 ± 0.23</td>
</tr>
<tr>
<td><strong>Sternberg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>3.10 ± 1.15</td>
<td>2.97 ± 0.64</td>
</tr>
<tr>
<td>Left IFG</td>
<td>2.15 ± 0.74</td>
<td>1.97 ± 0.47</td>
</tr>
<tr>
<td>Right IFG</td>
<td>2.27 ± 0.94</td>
<td>2.43 ± 0.64</td>
</tr>
<tr>
<td>Left MFG</td>
<td>2.75 ± 0.95</td>
<td>2.81 ± 0.96</td>
</tr>
<tr>
<td>Right MFG</td>
<td>2.74 ± 1.10</td>
<td>2.59 ± 0.84</td>
</tr>
</tbody>
</table>

ROIs, regions of interest; ACC, anterior cingulate cortex; HC, hippocampus; LG, lingual gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus.

---

**Figure 4.**

Functional connectivity in relation to performance on the digit-symbol substitution test (DSST) (A) and word recognition (B) in patients. The schematic illustration shows the selected regions of interest in the Sternberg paradigm and all possible connections (thin lines). The thick lines indicate the connections that correlate positively with the test scores. The intermediate line indicates a trend toward significant correlation ($p = 0.08$). ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; l, left; r, right.
these lower prefrontal connections were associated with worse performance on word recognition.

Neuronal correlate for working memory dysfunction

The results of this study confirm the importance of network functionality for working memory functions and the possibility that epilepsy can alter these networks. Interestingly, patients display difficulties in a range of memory functions with poorer performance for both classical (mesio)temporal functions (recognition), as for prefrontal tests (transient and more stable components of working memory). However, these memory deficits could not be linked to hippocampal abnormalities or alterations in the hippocampal network. Instead, in the patient group, a reduction in the synchronicity of cerebral regions within the prefrontal network was associated with dysfunction of the central executive. No comparable correlation could be demonstrated for the functional connectivity values and the tests for short-term memory. One could argue that good functioning of the central executive serves as a gateway for other cognitive functions. The differences in performance on tests for short-term memory are then a consequence of impairments in working memory, specifically in the central executive. However, our data are not sufficient to confirm such an assumption. Because prefrontal functional connectivity decreased with poorer working memory performance, it may reflect a neuropathologic or an insufficient compensation process. Furthermore, our findings support the concept that epilepsy as the underlying condition influences the prefrontal network. This influence does not solely depend on hippocampal abnormalities, since patients with symptomatic lesions (e.g., mesiotemporal abnormalities) were excluded. In addition, network changes did not depend on the side or site of seizure focus.

Comparison with previous studies

Memory dysfunction

The finding that patients performed worse on all neurocognitive tests is in keeping with former investigations which demonstrated a variety of memory deficits (Bengner et al., 2006; Hermann et al., 2006). Moreover, memory impairment and decline are more pronounced in subgroups with TLE, especially those with lower baseline IQ (Hermann et al., 2006). Memory deficits have been described shortly after the occurrence of temporal seizures (Helmstaedter et al., 1994). This cannot explain the differences between our patients and controls, since seizures did not occur on the day of neurocognitive assessment.

Brain activation

Studies with patients with mesiotemporal sclerosis (Dupont et al., 2002; Cheung et al., 2006) or symptomatic lesions such as gliomas (Cheung et al., 2006), demonstrated lower cerebral activation as well as poorer memory performance in TLE patients than controls. In patients with hippocampal sclerosis, a prefrontal hypoactivation and more activation in the occipitoparietal regions were suggested to be an alteration of temporoparietal connectivity (Engelsen et al., 2006). In the current study, no significant between-group differences were found regarding fMRI activation maps related to memory tasks, which confirms the normal functionality of the hippocampi in the selected patients.

Network integrity

Our findings that reduced functional connectivity in the engaged network of the patients is associated with poorer working memory performance, is in line with previously demonstrated changes in frontal and temporal networks related to memory dysfunction. However, the novelty of the current study lies in the exclusive selection of patients without any visible lesions on 3T MRI, whereas others have reported on patients with (mesio)temporal MRI abnormalities. In a surgical population with unilateral hippocampal sclerosis, stronger preoperative intrahemispheric functional connectivity was associated with better task performance preoperatively, and more verbal learning decline postoperatively (Wagner et al., 2007). Poorer quality of autobiographical memory in patients with TLE was reported in combination with a downregulation of cerebral activity in the entire autobiographical memory network (Addis et al., 2007). With functional connectivity analysis an alteration of this network was demonstrated, with bypassing of the left hippocampus and increasing connection strengths between other surrounding areas. Other recent studies in lesional TLE have demonstrated reduced functional connectivity in the so-called default network (Frings et al., 2009), between bilateral medial temporal lobes and left orbitofrontal gyrus (Voets et al., 2009), and a shift of levels of functional connectivity from the ipsilateral to the contralateral temporal region (Bettus et al., 2009). In the latter study, working memory performance correlated with functional connectivity between anterior and posterior parts of the right hippocampus. Impairment of functional connectivity networks has also been demonstrated in language networks (Waites et al., 2006) and correlated with language impairment (Vlooswijk et al., 2010). In general, network integrity appears to be important for more cognitive functions than memory alone, such as for language and information processing. In this study, this is reflected by the association of performance on the DSST—a test with engagement of multiple cognitive processes reflecting especially the central executive component of working memory—and the integrity of the prefrontal network.

Relation with clinical observations

In this study, patients were included independent of whether they experienced memory problems or not. Although the patient group performed evidently worse on
all memory tests, patients’ performance ranged from obviously disturbed to completely normal. It would have been interesting to relate the objective memory tests and fMRI results to subjective memory appraisal. In clinical practice, many patients complain about memory, but detailed neuropsychological assessment does not always demonstrate clear-cut memory deficits. Several explanations for the perception of poor cognitive skills have been proposed, such as the perception of gaps in experience due to amnesia in ictal and postictal periods, fluctuations in medication levels, and the high incidence of depression in refractory epilepsy (Thompson & Corcoran, 1992; Selwa et al., 1994). Previous studies have demonstrated that other cognitive functions, such as language skills and access to vocabulary, are also likely to be involved in subjective memory problems (Helmstaedter & Elger, 2000). Another clinical impression is that many patients with memory problems exhibit mental slowing. These observations potentially support the concept that principally the prefrontal networks are dysfunctional, with interruption of cognitive functions, which are commonly localized in the prefrontal regions.

**Methodologic issues**

In the current study we found that reduced functional connectivity in a verbal working memory (Sternberg) paradigm negatively correlated with reduced scores on the DSST test in patients with epilepsy, but not in healthy controls. Therefore, this effect appeared to be disease specific. For the arithmetic test the opposite was found: a positive correlation between the functional connectivity and the arithmetic scores in the healthy controls, but not in the patients. The absence of any significant effect in the patients cannot be inferred as disease specific. The presence or absence of correlations between the functional connectivity and specific neuropsychological tests needs to be investigated in more detail. In this study only two memory paradigms were utilized for the fMRI and six tests were used in the neuropsychological exam. Further research is required utilizing more specific memory paradigms to reveal which regional functional connections in the brain explain the impairment of certain memory processes and the nature of the relation between neuropsychological performance and the strength of functional connections in healthy control subjects.

**Conclusions**

This study suggests an important role for functional connectivity in the prefrontal networks on working memory performance in patients with epilepsy. For the first time, a correlation between prefrontal network changes and working memory was demonstrated in patients with both temporal and extratemporal epilepsy without symptomatic lesions or mesiotemporal sclerosis. Our findings stress the influence of epilepsy as such on prefrontal network integrity regardless of a structural lesion. Whether there is a causal relationship between epilepsy, prefrontal network dysfunction, and memory deficits, or all these entities are the result of yet another—still unknown—pathologic mechanism, remains to be elucidated.

**Acknowledgments**

The authors are grateful to Leonie Diepman and colleagues of the Behavioral Science Department in Epilepsy Centre Kempenhaeghe for their great efforts to perform all neuropsychological assessments. This study is supported by grant number 06-02 of the National Epilepsy Foundation (NEF), Zest, The Netherlands.

**Disclosure**

The authors declare 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**


**Supporting Information**

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

**Table S1.** Characteristics of patients with epilepsy and healthy controls.

**Appendix S1.** Description of fMRI paradigms.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.