Chronic epilepsy is frequently accompanied by serious cognitive side-effects. Clinical factors are important, but cannot account entirely for this cognitive comorbidity. Therefore, research is focusing on the underlying cerebral mechanisms to understand the development of cognitive dysfunction. In the past two decades, functional MRI techniques have been applied extensively to the study of cognitive impairment in chronic epilepsy. However, because of wide variation in study designs, analysis methods, and data presentation, interpretation of these studies has become increasingly difficult for clinicians. In patients with localisation-related epilepsy, whether findings of functional MRI represent the underlying neuronal substrate for cognitive decline remains a subject of debate.

Introduction

Although seizures are the most prominent feature of epilepsy, many patients rank cognitive impairment highest on their list of complaints (table 1).1-4 The cognitive disorders reported in epilepsy cover essentially all cognitive domains. In temporal lobe epilepsy (TLE), memory deficits of all kinds have been described, especially impairment of verbal long-term consolidation and retrieval, verbal learning, short-term or working memory,5 and spatial memory.6 However, other neurological functions can also be affected in focal epilepsy, causing frontal lobe dysfunctions, such as problems with response inhibition, attention, planning, and psychomotor speed.7 Furthermore, language deficits, such as poor naming and fluency skills and disturbance of global intelligence, can occur.8,9 Most of this information is from studies in patients with TLE because this disorder is the most frequent cause of medically refractory epilepsy, and epilepsy surgery is often considered in these patients. In preoperative screening, a large amount of data is collected, with extensive information about seizure focus, language dominance, and neuropsychological profile.10

Naturally, much research has focused on the factors contributing to the development of cognitive dysfunction. Ultimately, if a clinical factor could be identified to play a major part in this development, clinicians might stop or change this process by tailoring the treatment of their patients. In this respect, research has focused on the role of seizure frequency, seizure severity,9 chronic antiepileptic drug use,11 and persistent interictal epileptic brain activity.12 Other factors that could affect cognition in epilepsy are seizure-induced head trauma,13 young age at onset of epilepsy,14 and long duration of epilepsy.1 However, since cognitive deficits can be already present in newly diagnosed, untreated patients,14,15 clinical factors, such as high frequency or severity of seizures, are unlikely to account completely for the reported cognitive disorders. The focus of research has therefore changed to the neuronal mechanisms responsible for cognitive deficits.

Since the introduction of MRI, several techniques have been applied in research focusing on the cerebral processes responsible for cognitive decline. Functional MRI (fMRI) has been used extensively to investigate cognitive deficits because it can combine data from cognitive fMRI studies with neuropsychological data to display the dynamics of cognitive processes. In the past two decades, many fMRI studies have been published. However, most studies focus on a fairly specific area of cognitive functioning or the brain. In this Review, we summarise and put into perspective research on fMRI abnormalities associated with cognitive deficits in localisation-related epilepsy, and discuss the extent to which fMRI findings represent the underlying neuronal substrate that might explain cognitive decline. Furthermore, we will discuss the limitations of fMRI techniques and make recommendations for future research.

fMRI activation patterns

fMRI has been used extensively in preoperative screening to predict possible postoperative cognitive deficits, so many patients with localisation-related epilepsy have undergone both fMRI and neuropsychological assessment.16 These data can be analysed to investigate the extent to which fMRI patterns correlate with cognitive tests. In this Review, we will focus on fMRI studies that specifically mention the correlation between neuropsychological data and fMRI activation patterns (table 2).16-23

Theoretically, four possible activation patterns can be recorded in investigation of cognitive deficits in patients with epilepsy. First, activation patterns could be similar for patients and healthy controls despite cognitive differences; these types of results are not likely to be published. Second, an absence or decrease in activation could be recorded in areas that are activated in healthy controls. Third, more activation could be recorded in patients than in healthy controls, either in or outside the brain regions activated in controls. Fourth, the second and third patterns could be combined, resulting in less activation in one area and more activation in another, suggesting a shift of activation. The second and fourth patterns of activation predominate in studies in which fMRI abnormalities are described in relation to cognitive data. Depending on whether cognitive deficits are present or not, the changes in activation patterns can be interpreted as either a functional or dysfunctional process. A functional process represents...
an effective, possibly compensatory mechanism to preserve cognitive functioning. A dysfunctional process represents a pathological or at least an insufficient compensatory mechanism.

Memory

Most studies included in this Review were done in patients with unilateral TLE, and many of these used verbal memory tasks,20–23 or visual complex-scene encoding tasks.24–29 In one study, patients with left-sided TLE showed activation of the left dorsolateral prefrontal cortex in addition to the bilateral activation of the parahippocampal gyri seen in healthy controls.29 In subsequent studies with overlapping samples, patients were rescanned 24 h later during a verbal memory retrieval task, and, unlike controls, they did not have increased activation of the right hippocampus or parietal brain areas.29 Interestingly, patients with right-sided TLE also performed more poorly on the verbal memory task than did controls, and this was associated with lower functional activation in the left mesiotemporal lobe.29 Although the sample sizes in these studies were small, these data suggest that functional activation is reallocated in patients with left TLE, and patients with right TLE have a bilateral functional impairment. However, the data should be interpreted with care, since fMRI data were only correlated with performance during the fMRI task, and not with results of formal neuropsychological tests. Furthermore, patients with left TLE were included in these studies only when verbal memory dysfunction was present, and fMRI activation patterns could have been affected by the difference in task performance between patients and controls.

Similar results were reported in a somewhat larger population of patients with left and right TLE, in which better memory was correlated with greater activation in the mesial temporal lobes.29 However, no left-right differentiation was noted for verbal and visual memory. In a subsequent study, less activation in the damaged left hippocampus was correlated with worse verbal memory in a group of patients with left TLE.29 A similar effect was recorded for non-verbal memory in patients with right TLE: the greater the activation of the right hippocampus, the better the non-verbal memory performance.29 Even though this study was small, the findings suggest that reorganisation of memory functions to the undamaged mesiostemporal lobe is an inefficient process. This explanation would account for the fact that patients with better preoperative memory functioning, and probably a better functioning hippocampus on the side of the seizure focus, are most at risk of postoperative impairment when the epileptogenic hippocampus is removed. In a large surgical population, better preoperative verbal memory was correlated with greater left hippocampal activation for word encoding in patients with left TLE (figure 1).29 In patients with right TLE, greater right hippocampal activation during face encoding was correlated with better visual memory. Furthermore, higher preoperative activation of the posterior part of the ipsilateral hippocampus in left and right TLE was correlated with better verbal and visual memory scores, respectively, after anterior temporal lobe resection (in which only the anterior part of the hippocampus is resected).

These results support the so-called functional adequacy model, which suggests that postoperative memory function is better preserved with recruitment of ipsilateral posterior hippocampal networks than with recruitment of the contralateral hippocampus. Indirect support for this theory comes from another surgical study, in which higher preoperative activation in the left hippocampal region in patients with left TLE correlated with greater postoperative visual memory decline;29 a direct comparison between fMRI activation and preoperative memory performance was not done. In a mixed population of patients with localisation-related epilepsies, patients with a left-lateralised seizure focus showed a shift towards right-lateralised activation.29 To a lesser extent, a similar effect was seen for patients with a right-hemisphere seizure focus, who had more left-lateralised activation. However, for both patient groups, better verbal memory was associated with greater left-lateralised mesial temporal lobe activation. Hence, the shift of activation from the left to the right hemisphere was not sufficient to maintain normal verbal memory.29

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<table>
<thead>
<tr>
<th>Patients reporting moderate-to-severe disorders</th>
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<tr>
<td><strong>Mental health</strong></td>
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<tr>
<td>Fear of recurring seizures</td>
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<tr>
<td>Change of outlook for future plans and ambitions</td>
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<tr>
<td>(Fear of) stigma</td>
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<td><strong>General health</strong></td>
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<tr>
<td>Lack of energy</td>
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<td>Side-effects or adverse effects from an antiepileptic drug</td>
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<tr>
<td><strong>Cognitive functions</strong></td>
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<tr>
<td>Impaired memory; as an adverse effect of an antiepileptic drug</td>
</tr>
<tr>
<td>Impaired concentration; as an adverse effect of an antiepileptic drug</td>
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<tr>
<td>Impaired thinking; as an adverse effect of an antiepileptic drug</td>
</tr>
<tr>
<td><strong>Lifestyle</strong></td>
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<tr>
<td>Impaired ability to drive a car</td>
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<tr>
<td>Adverse effect on leisure pursuit</td>
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<tr>
<td><strong>Relationships</strong></td>
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<tr>
<td>Adverse effect on relations with family and close others</td>
</tr>
<tr>
<td>Negative effect on sex life</td>
</tr>
<tr>
<td>Concerns about having children</td>
</tr>
<tr>
<td><strong>Social activities</strong></td>
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<tr>
<td>Adverse effect on school performance</td>
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<tr>
<td>Adverse effect on job performance</td>
</tr>
</tbody>
</table>

Community-based postal survey in 1023 patients with epilepsy.1 Postal survey in 192 patients with recent diagnosis of epilepsy (<3 years).2 Postal survey in more than 5000 members of epilepsy support groups.3

Table 1: Major disorders in patients with epilepsy
Recognition of faces with negative emotional expressions is less frequently studied than are other types of non-verbal memory. In a subgroup of patients with right-sided TLE of early onset, impaired recognition of facial expressions correlated with the absence of activation in the inferior frontal cortex and occipitotemporal cortex bilaterally.\textsuperscript{13}

By contrast with most studies describing dysfunctional changes in activation patterns—ie, not sufficient to maintain normal memory—some studies support the theory that functional activation changes are an efficient compensatory mechanism. For instance, Engelsen and colleagues\textsuperscript{23} did not record any behavioural differences between patients and controls during a visuospatial encoding and retrieval test. They did, however, show altered fMRI activation patterns, with more occipito-parietal activation in patients and more prefrontal and parietal activation in healthy controls. The investigators postulated that patients showed compensatory activation in the occipito-parietal parts of the brain, but, again, no extensive neuropsychological assessment was done to test whether memory was indeed undisturbed in the patient group. A similar study design was applied in a small population in which both patients and controls had intact verbal memory,\textsuperscript{14} and patients showed more activation in some regions, which was interpreted as a compensatory mechanism to maintain normal verbal memory.

### Language processing

Language representation and its possible reorganisation are of major importance in preoperative screening. In several studies, activation patterns in response to language tasks have been correlated with language performance. During two linguistic fMRI tasks, functional activation patterns substantially overlapped in patients with unilateral TLE. However, in patients with left-sided TLE, the left dorsolateral prefrontal cortex had greater activation than in healthy controls, as well as increased signal change in the left inferior frontal and right middle temporal gyri.\textsuperscript{28} Surprisingly, only the patients with right TLE had poorer performance on the linguistic tasks than did controls, as well as decreases in right superior temporal activation. The investigators argued that the higher left frontal activity in left TLE suggested a functional reorganisation of

The table presents the study groups, fMRI test, cognitive tests, major outcomes, and interpretation for different conditions.

**Table**

<table>
<thead>
<tr>
<th>Study groups</th>
<th>fMRI test</th>
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<th>Major outcomes</th>
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<td><strong>Memory</strong></td>
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<td>Left mesial TLE with HS (n=7), controls (n=10)</td>
<td>Verbal memory</td>
<td>Behavioural performance\textsuperscript{1}</td>
<td>Worse performance of patients; activation of left dorsolateral prefrontal cortex in patients</td>
<td>Reallocation of functional activation is an inefficient process</td>
</tr>
<tr>
<td>24 h delayed verbal memory retrieval</td>
<td>Behavioural performance</td>
<td></td>
<td>Worse performance of patients; substantial decrease of activation in neocortical, hippocampal, and parahippocampal regions in patients</td>
<td>Dysfunctional activation patterns</td>
</tr>
<tr>
<td>Left mesial TLE with HS (n=7), right mesial TLE with HS (n=7), controls (n=10)</td>
<td>Verbal memory</td>
<td>Behavioural performance</td>
<td>Worse performance of patients with right TLE; lower activation of the left hemisphere, mainly in mesiotemporal regions, in patients with right TLE</td>
<td>Dysfunctional activation patterns</td>
</tr>
<tr>
<td>TLE (n=23), varying aetiologies of mesial and lateral, controls (n=23); mixed adults and adolescents</td>
<td>Visual memory (complex-scene encoding)</td>
<td>Behavioural performance; verbal and visual memory tests</td>
<td>Less activation in temporal lobes in patients, most pronounced in ipsilateral hemisphere; more activation in mesiotemporal regions in patients with better memory performance</td>
<td>Dysfunctional activation patterns</td>
</tr>
<tr>
<td>Mesial TLE with HS (n=11), controls (n=10)</td>
<td>Visual spatial memory and encoding</td>
<td>Behavioural performance</td>
<td>More activation in posterior neocortical regions in patients; no behavioural differences</td>
<td>Compensatory reallocation of functional activation</td>
</tr>
<tr>
<td>Verbal and visual memory (word, picture, and face encoding)</td>
<td>Behavioural performance; verbal and figure recall tests</td>
<td></td>
<td>Greater activation in left hippocampus in patients with left TLE and better verbal memory performance; greater activation in right hippocampus in patients with right TLE and better non-verbal memory; greater activation in contralateral hippocampus in patients with worse memory performance</td>
<td>Reallocation of functional activation is an inefficient process</td>
</tr>
<tr>
<td>TLE (n=49), controls (n=25)</td>
<td>Visual memory (complex-scene encoding)</td>
<td>Story recall test</td>
<td>Greater activation in left hippocampal region in patients with better memory, independent of seizure focus</td>
<td>Reallocation of functional activation is an inefficient process</td>
</tr>
<tr>
<td>Mesial TLE, n=3 anterior temporal, controls (n=20)</td>
<td>Verbal and visual memory (word, picture, and face encoding)</td>
<td>Extensive neuropsychological assessment \textsuperscript{1}</td>
<td>Left hippocampal activation correlated with better preoperative verbal memory in patients with left TLE; right hippocampal activation correlated with better preoperative visual memory in patients with right TLE; preoperative ipsilateral posterior hippocampal activation correlated with better postoperative memory scores</td>
<td>Intrahemispherical reallocation of functional activation is efficient by contrast with interhemispherical reallocation</td>
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(Continues on next page)
language representation. However, the linguistic tasks might not have been sensitive enough to detect clinically relevant language deficits, and therefore the results should be interpreted with care.

In a heterogeneous preoperative population, patients with worse performance during a linguistic fMRI task—ie, those with lower accuracy and longer reaction times—showed greater activation in the inferior frontal region and less activation in the temporoparietal region than did patients who performed better on this task.  

Language functions, such as verbal fluency and naming scores, correlated with degree of language reorganisation and side of seizure focus in a large, heterogeneous group of patients: good preservation of language functions was associated with normal language representation, expressed as high asymmetry indices, in patients with a right-sided seizure focus, but with atypical language representation and low asymmetry indices in those with a left-sided focus. Similarly, in a small population of patients with TLE, atypical language representation was more frequently recorded in left TLE than in right TLE. Patients with atypical language representation performed better on language tests than did those with normal language representation, which is indicative of an adaptive, compensatory mechanism.

In Wong and colleagues’ study, greater bilateral activation in the typical language regions was correlated with better language in patients with right TLE. The researchers suggested that a similar effect was not recorded in the left TLE group because language processing had been reallocated to regions other than those investigated.

<table>
<thead>
<tr>
<th>Study groups</th>
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<th>Cognitive tests</th>
<th>Major outcomes</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
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<tr>
<td>Billingsley et al.</td>
<td>TLE (n=17), n=4 unspecified, controls (n=11)</td>
<td>Language (orthographic, phonological, and semantic decision)</td>
<td>Behavioural performance</td>
<td>Greater left prefrontal activation in patients with left TLE; worse performance and decreased right superior temporal activation in patients with right TLE</td>
</tr>
<tr>
<td>Berl et al.</td>
<td>LRE (n=50, mix of temporal, frontal, fronotemporal, parietal, and multifocal), controls (n=33); adults and children</td>
<td>Language (response naming)</td>
<td>Intelligence, memory, naming, and fluency tests</td>
<td>Atypical language organisation (low asymmetry indices) associated with higher IQ and naming scores in patients with left seizure focus; high asymmetry indices correlated with higher IQ and verbal fluency in patients with right seizure focus</td>
</tr>
<tr>
<td>Thivard et al.</td>
<td>TLE (n=26, both mesial and lateral), controls (n=17)</td>
<td>Language (semantic fluency, covert sentence repetition, and story listening)</td>
<td>Intelligence, memory, and fluency tests</td>
<td>Frequent atypical language representation in left TLE, better language performance in patients with atypical language representation</td>
</tr>
<tr>
<td>Weber et al.</td>
<td>LRE (n=195, TLE and extratemporal not specified)</td>
<td>Language (semantic decision)</td>
<td>Behavioural performance</td>
<td>Subgroup of worst performing patients (n=49): more inferior frontal activation and less temporoparietal activation</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>Mesial TLE (n=23), controls (n=11)</td>
<td>Language (verb generation)</td>
<td>Naming, fluency, and auditory processing</td>
<td>Bilateral activation of language areas in patients; better language performance and greater activation in bilateral language areas in patients with right TLE; this relation is absent in patients with left TLE who also show activation outside the typical language areas</td>
</tr>
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</table>

**Other**

<table>
<thead>
<tr>
<th>Study groups</th>
<th>fMRI test</th>
<th>Cognitive tests</th>
<th>Major outcomes</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>Meletti et al.</td>
<td>Right mesial TLE of early onset (n=4), left and right mesial TLE of late onset (n=8), controls (n=14)</td>
<td>Fearful face recognition</td>
<td>Emotion recognition test</td>
<td>Impaired recognition of negative emotions in right TLE of early onset; bilateral inferior frontal and occipitotemporal activation is absent in patients with right TLE of early onset</td>
</tr>
</tbody>
</table>

If not stated otherwise, studies included adult patients and controls. TLE—temporal lobe epilepsy (both hemispheres). HS—hippocampal sclerosis. LRE—localisation-related epilepsy. IQ—intelligence quotient. *Studies with (partly) overlapping study populations. †Performance during the fMRI cognitive task, assessed during the scanning procedure or with tests after scanning. ‡Neuropsychological assessment covering a broad range of cognitive domains, including measures of intelligence, language, visuoperception, memory, executive function, and motor function.

Table 2: Functional MRI studies investigating activation patterns in relation to cognitive performance

Clinical and theoretical implications and limitations

Differences in study populations, fMRI cognitive tasks, and outcome measures make identification of a general effect of localisation-related epilepsy on fMRI activation maps and cognition extremely difficult. Some studies have included patients partly on the basis of the presence of cognitive deficits, but altered functional activation is difficult to correlate directly with these deficits. In others, poorer neuropsychological performance and altered functional activation are reported, but direct correlations were not included. In several studies, the fMRI activation patterns have been correlated with the behavioural data obtained during fMRI scanning, but these data might not be as sensitive as the results of formal neuropsychological testing for detection of cognitive deficits. Furthermore, most of these studies investigated small populations with epilepsy.
Nevertheless, most studies support one of two possible processes in patients with localisation-related epilepsy: activation is decreased in the regions that are activated in healthy controls and is associated with cognitive deficits, or activation is intrahemispherically or interhemispherically shifted from the normally activated regions to other cerebral regions. Data are contradictory as to whether this shift is functional (with preserved cognitive abilities) or dysfunctional (with cognitive impairment). Most studies support a dysfunctional shift: for example, in a small heterogeneous population with epilepsy, a shift from frontotemporal to prefrontal activation had some correlation with cognitive decline.\(^3^5\) Conversely, associations between reported functional activation patterns and cognitive deficits do not necessarily signify a causal relationship between both factors—differences in fMRI activation patterns and cognitive abnormalities could be the result of an unknown third, aetiological factor.

In daily practice, fMRI activation maps can be applied in preoperative screening to identify patients with high risk of postoperative cognitive deficits. From the studies reviewed, we conclude that patients with the most interhemispheric or intrahemispheric reorganisation of cognitive processes are least likely to have poor postoperative cognitive outcome. However, these patients are more likely to have poorer preoperative cognitive function. Present fMRI techniques are not yet sensitive enough to be used as a diagnostic or prognostic instrument in individuals with cognitive disorders.

**Functional connectivity**

**Analysis methods**

In the past ten years, research has started to focus on the function of cerebral networks in epilepsy. Cognitive functions depend on the orchestrated action of several rather than isolated brain regions. For that reason, exploration of the integrity and organisation of cerebral networks could reveal more about cognitive decline than could study of activation patterns. For TLE, abnormal function seems to extend from the epileptic zone in the temporal lobe to connected regions within and outside the temporal lobe.\(^3^6\) Increasing interest is being given to the effects of dysfunctional networks on cognition in epilepsy.

With fMRI, different analysis techniques have been applied to measure functional connectivity. First, the extent to which the time course of the fMRI signal is correlated between different cerebral regions can be measured.\(^3^7\) High correlation coefficients are indicative of high functional connectivity between the selected regions. This technique has been used with resting-state fMRI to investigate the language-processing network, and showed that patients with left TLE had a disruption to their language network compared with controls.\(^3^8\) Another study used a visual memory task to investigate the default mode network (ie, a group of brain regions that are more active in passive than in active tasks) and the role of the precuneus (part of the superior parietal lobule).\(^3^9\) Patients with left TLE had weaker functional connectivity between the precuneus and ipsilesional lateral temporal cortex and hippocampus, which the researchers interpreted as damage to the network distant from the site of seizure focus.

A second method to investigate functional connectivity within a network is independent component analysis. The brain is divided into different networks (components) of brain regions on the basis of the extent to which the signal time courses of these regions coincide,\(^4^0\) and the
contribution of individual brain regions to this network can then be calculated. This technique was used in patients with unilateral TLE to select the component that best fitted the template of the default network. Patients with left-sided TLE had weaker functional connectivity in the left mesial temporal structures, whereas patients with right-sided TLE had lower connectivity in both mesial temporal lobes. In a study of the networks for auditory, sensorimotor, and visual information processing in patients with bilateral TLE, patients had lower auditory and sensorimotor functional connectivity than did controls. By contrast, within the visual network, patients had stronger functional connectivity in the primary visual cortex and a corresponding decrease in higher order visual cortex.

A third technique to investigate functional connectivity does not depend on previous selection of the network of interest. The brain is divided into several regions—eg, 90 regions with anatomical automatic labelling—and graph theoretical analysis is used to investigate the topology of the network (for a review, see Stam and Reijneveld) and estimate whether the brain exhibits small-world characteristics or represents a random network. Small-world characteristics refer to widespread local clustering, combined with some long-distance connections for rapid information transfer throughout the overall network. Random networks are supposed to be less efficient in global communication than are small-world characteristics, and have been associated with lower intelligence in healthy adults. With this technique, patients with bilateral TLE were shown to have more randomly structured networks than were healthy controls. Notably, combination of studies investigating small-world characteristics could be used to explore the possible relation between cognitive dysfunction and altered organisation of cerebral networks in patients with chronic epilepsy.

**Combination of functional connectivity and cognitive assessment**

According to the abovementioned studies, network functionality is decreased in TLE, but the effect of these network changes on cognitive functioning has not been investigated. In most studies addressing both functional connectivity and cognitive functions, a predefined network of interest was used and the correlation coefficients of signal time courses within this network were compared with the results from cognitive tests.

In a surgical population of patients with TLE, higher preoperative functional connectivity between the hippocampus and the superior temporal gyrus was noted for patients who had decreased verbal learning postoperatively than for those who remained stable or improved postoperatively. The investigators suggested that greater functional connectivity is indicative of higher functional network integrity. In a small sample of patients with left TLE, functional connectivity within the temporal lobes was investigated. Compared with controls, patients had less functional connectivity within the left mesiotemporal structures. Furthermore, patients with greater functional connectivity within the right hippocampus had better memory than did those with less functional connectivity, which was interpreted as a compensatory mechanism. By contrast, in patients with unilateral TLE, higher functional connectivity between both hippocampi was not associated with better test performance than in those with low functional connectivity between the hippocampi.

In the autobiographical network, the connections with the left hippocampus were weaker in patients with left TLE than in controls. Conversely, functional connectivity between regions outside the hippocampus was higher in these patients than in controls. This bypassing of the damaged hippocampal node was interpreted as a compensatory mechanism, especially because patients had only a mild deficit of episodic autobiographical memory. In Vlooswijk and colleagues’ study of patients with cryptogenic localisation-related epilepsies, impairment of language function was associated with decreased functional connectivity within the prefrontal network. With independent component analysis, lower functional connectivity in the dorsal attention network was associated with worse attention in patients with bilateral TLE. Moreover, better attention was correlated with stronger connectivity in the right frontal eye field, indicating a compensatory mechanism.

**Structural and functional connectivity**

Although fMRI can be used to measure whether two brain regions are functionally connected by correlation of the signal time courses of these regions, this functional connection does not necessarily imply a structural connection. To investigate structural connectivity, diffusion-tensor imaging can be used. With this MRI technique, measurement of the diffusion of water molecules in brain tissue can be used to visualise cerebral white matter tracts (magnetic resonance tractography). In patients with TLE, functional language lateralisation correlates with structural lateralisation. Both functional and structural connections were greater in the right hemisphere in patients with left TLE than in patients with right TLE and controls, but the reverse was seen in patients with right TLE (figure 2). A similar structural-functional coupling (ie, left lateralisation) was seen in the arcuate fasciculus—a white matter tract connecting the anterior and posterior language regions—of patients with right TLE, but not in patients with left TLE.

Some studies have combined results of diffusion-tensor imaging with neuropsychological data. In patients with left TLE, the integrity of the uncinate fasciculus—a major white matter tract connecting anterior temporal and frontal lobes—was related to memory performance. In a small TLE sample, higher lateralisation of structural connections from the inferior frontal gyrus was correlated with better language performance. For patients with
TLE and interictal psychosis, poorer neuropsychological performance was related to disturbed frontotemporal white matter integrity, as indicated by fractional anisotropy measures derived from diffusion-tensor imaging. In a study comparing patients with both left and right TLE versus controls, poor verbal memory and naming were correlated with structural damage to many fibre tracts, especially in the language-dominant hemisphere. This effect was specific to selected white matter tracts because cognitive performance was not related to the integrity of a motor white matter tract. However, the sample size was small and heterogeneous, with inclusion of some patients after anterior temporal lobe resection.

Other techniques to study functional connectivity
fMRI is useful for study of functional connectivity because of its high spatial resolution. However, temporal resolution is low by contrast with other techniques, such as magnetoencephalography and electroencephalography (EEG). With these techniques, functional connectivity can be measured by correlation of time series of regions of neuronal activity in terms of wavelet frequencies. In epilepsy, EEG connectivity analyses have been used to study epileptogenic networks, indicating a localised increase in synchronisation during seizures and decreased functional connectivity in the interictal state. Recent technological advances have allowed the simultaneous acquisition of EEG and fMRI, which yields a powerful strategy combining the high spatial resolution of fMRI with the high temporal resolution of EEG. The interesting theory that these changes in synchronisation and functional connectivity might participate in the development of interictal cognitive deficits in epilepsy has, however, not been tested.

Clinical and theoretical implications and limitations
Functional connectivity analysis is a fairly new, but promising, method to study cognitive dysfunction in epilepsy. Studies with this technique all point to a disruption of functional networks in epilepsy, either in a small region or in the whole brain. However, this conclusion is based on mean results for patient groups, which limits application to individual patients with cognitive disorders.

Whether functional connectivity studies are better done with task-related or resting-state fMRI is not yet certain. With resting-state fMRI, measurement of spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal provides an indication of spontaneous neuronal activity. Accumulating evidence suggests that spontaneous BOLD fluctuations map specifically to functionally related brain regions and relate to known anatomical networks. Since resting-state fMRI does not depend on task performance, it can be applied more extensively than can task-related fMRI. However, resting itself is also associated with a certain amount of attention, hence a certain cognitive state, which is indicated by activation of the typical default network.

Different analysis methods have been used to investigate functional connectivity. Most studies have used analysis methods to explore functional connectivity within a predefined network, including regions known to participate in a specific cognitive function. Although this approach is rational for exploration of potentially disrupted networks, it cannot show network reorganisation associated with brain regions excluded from the analysis. Furthermore, most studies describe disrupted functional connectivity in terms of decreased statistical interdependencies between signal time courses of different brain areas. However, analysis of fMRI data to construct a hierarchical map and identify

Figure 2: Example of functional MRI activation patterns for verb generation and reading comprehension in controls (A, B) and patients with left-sided (C, D) or right-sided (E, F) temporal lobe epilepsy
Significant regions are superimposed onto the normalised mean structural MRI scans from all controls or patients. The left side of the brain is shown on the left side of the images. For verb generation, controls (A) and patients with right TLE (E) show activation of the left inferior frontal gyrus, whereas patients with left TLE (C) show bilateral activation of the inferior frontal gyrus. For reading comprehension, controls (B) and patients with right TLE (F) show bilateral activation of the superior temporal gyrus, whereas patients with left TLE (D) show activation of the left superior temporal gyrus. TLE=temporal lobe epilepsy. Reproduced from Powell and colleagues, with permission from Elsevier.
which regions are most closely related is more complicated. Attempts to explore hierarchical relations within a network also depend on an a-priori definition of regions of interest. On the contrary, with independent component analysis, predefined network of interest is not needed. However, the researcher needs to decide which one of the networks identified by mathematical algorithms is a neuroanatomical system, thereby introducing a selection bias. Also, disentangling all physiological (respiratory, cardiac, and vasomotion) and motion confounds through preprocessing is very challenging, and remains a major difficulty. Graph theoretical analysis offers the opportunity to study the entire brain network in terms of effective network topology. This fairly new technique is developing quickly and its applicability in epilepsy and cognition needs further exploration in the near future.

Conclusions and future directions
Cognitive dysfunction in localisation-related epilepsy is associated with changes in functional activation patterns and decreased functional connectivity within selected brain networks. fMRI is especially suited to research of cognitive consequences of epilepsy because it can display the dynamics of cognitive processes. However, direct comparison between most studies is complicated because of differences in study populations, fMRI tasks, and methods for data analysis. Research is now focusing on the effect of epileptic processes on localised and global cerebral networks.

On the basis of existing knowledge of cerebral processes underlying cognitive dysfunction in epilepsy, future studies are needed to address some unanswered questions. fMRI could be used to investigate chronic extratemporal epilepsies in large populations, and thereby establish whether knowledge about patients with TLE can be extended to patients with other epilepsy types or whether other cerebral processes are occurring. The role of altered cerebral networks in the development of cognitive deficits in epilepsy needs extensive exploration. Ideally, longitudinal studies should be done to understand changes in network organisation in relation to cognitive functioning, with retesting intervals of several years. The fact that cognitive impairment is already present at onset of epilepsy in some patients implies that unknown, pathological cerebral processes have occurred. However, we have not identified any information about the order in which cognitive dysfunction, and structural and functional MRI abnormalities, occur. Study of large healthy populations to capture patients who develop chronic epilepsy is unfeasible, but researchers should try to study patients from the onset of disease. Preferably, the effect of clinical factors, such as antiepileptic drug use, epileptiform discharges, and seizure frequency, on these networks and cognition should be assessed. The association between cognitive outcome and other factors, such as age at onset of epilepsy, underlying pathology, seizure control with antiepileptic drugs or surgery, age at seizure control, and duration of epilepsy, needs investigation.

Information about factors that affect seizure control and cognitive outcome could provide a window of opportunity for effective seizure control to avoid cognitive impairment. The cerebral reserve theory—ie, higher intellect before morbidity can protect against cognitive decline—raises the issue of whether neurocognitive training at an early stage might reinforce existing networks and thus slow down or prevent cognitive decline. Identification of the cerebral mechanisms underlying the development of cognitive disorders, and the patients at risk for cognitive deterioration, might eventually lead to earlier therapeutic intervention than is available at present, with better cognitive outcome.

Contributors
MCGV searched for published reports and wrote the first draft of the Review. WHB, APA, and JFAJ helped to improve the first draft with addition of relevant reports, suggestions for structure of the Review, and the idea for schematic tables. MCFTMdK, HJMM and PAMH read the Review critically and made suggestions for improvements. WHB, APA, and JFAJ helped to improve the first draft with addition of relevant reports, suggestions for structure of the Review, and the idea for schematic tables. MCFTMdK, HJMM and PAMH read the Review critically and made suggestions for improvements.

Conflicts of interest
We declare that we have no conflicts of interest.

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