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Summary

Epilepsy syndromes are frequently accompanied by cognitive deficits. Temporal lobe epilepsy as well as resective surgery on the temporal lobe may affect cognitive function, in particular verbal and visual memory, but also working memory and naming ability. Epilepsy surgery offers an effective and safe treatment option for patients with medically refractory seizures rendering 60-70% of them seizure free. The goals of epilepsy surgery are to remove the brain areas generating the seizures without causing neuropsychological deficits such as language or memory dysfunction. This requires accurate localization of the brain areas generating the seizures ("epileptogenic zone"), as well as areas responsible for motor and cognitive functions, such as language and memory ("essential brain regions") during presurgical evaluation.

Functional magnetic resonance imaging (fMRI) is a useful tool to localize primary motor and somatosensory areas and to lateralize language and memory function; it also shows promise for predicting the effects of temporal lobe resection on memory and language function.

Functional MRI can be integrated with other MR imaging modalities to improve surgical strategies tailored to individual patients with regard to functional outcome, by virtue of definition of epileptic cerebral areas that need to be resected and eloquent areas that need to be spared.

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Key words: Epilepsy surgery, functional imaging, language, episodic memory, lateralization, hemispheric dominance, localization, anterior temporal lobe resection

Applications cliniques de l'IRMf du langage et de la mémoire chez les patients avec épilepsie

Les syndromes épileptiques sont fréquemment accompagnés par des déficits cognitifs. L'épilepsie du lobe temporale et, davantage, les résections chirurgicales touchant le lobe temporal peuvent altérer les fonctions cognitives, particulièrement la mémoire verbale et visuelle mais également la mémoire de travail et les capacités de dénomination. La chirurgie de l'épilepsie offre un traitement efficace et sûr pour les patients avec des crises pharmacorésistantes et rend 60-70% des patients libres de crise. Les buts de la chirurgie de l'épilepsie sont la résection des régions cérébrales qui génèrent les crises sans causer de déficits neuropsychologiques langagiers ou mnésiques notamment. Ceci nécessite une localisation précise des régions cérébrales qui génèrent les crises (« zone épileptogène ») ainsi que des régions responsables des fonctions motrices et cognitives (langage, mémoire: « régions cérébrales essentielles » durant l'évaluation préchirurgicale.

L'imagerie fonctionnelle par résonance magnétique (IRMf) est un outil utile pour localiser les régions motrices et somatosensorielles primaires et pour latéraliser les fonctions mnésiques et langagières. Cette technique est aussi prometteuse pour prédire les effects d'une résection temporale sur la mémoire et le langage.

L'IRMf peut être intégrée avec d'autres modalités d'imagerie IRM pour améliorer les stratégies chirurgicales individualisées en considérant le pronostic fonctionnel, en vertu de la définition des aires épileptiques cérébrales qui nécessitent d'être réséquées et des régions éloquantes qui doivent être épargnées.

Mots clés : Chirurgie de l'épilepsie, imagerie fonctionnelle, langage, mémoire épisodique, dominance hémisphérique, localisation, lobectomie temporale antérieure

Funktionelle MRT von Sprache und Gedächtnis in der Epilepsiediagnostik

Patienten mit Temporallappenepilepsie zeigen häufig kognitive Beeinträchtigungen, insbesondere Störungen des verbalen und visuellen Gedächtnisses, des Arbeitsgedächtnisses sowie Benennstörungen. Diese können durch einen operativen Eingriff verstärkt werden. Epilepsiechirurgie ist eine effektive und sichere Behandlungsmöglichkeit für Patienten mit medikamentös therapierefraktären Anfällen. Bei 60-70% dieser Epilepsiepatienten kann durch einen neurochirurgischen Eingriff Anfallsfreiheit erreicht werden. Ziel eines solchen epilepsiechirurgischen Eingriffes ist es, die epileptogene Zone zu entfernen, ohne postoperative, insbesondere neuropsychologische Defizite, wie zum Beispiel Sprach- oder Gedächtnisstörungen, zu verursachen.

Dementsprechend ist es notwendig, im Rahmen eines sorgfältigen, präoperativen Monitorings sowohl die Areale des Gehirns, von welchen die Anfälle ausgehen („epileptogene Zone"), als auch die Areale, die für motorische, Sprach- und Gedächtnisfunktionen verantwortlich sind („essenzielle Hirnareale") sorgfältig zu lokalisieren.

Grosse Fortschritte im Bereich der bildgebenden Verfahren haben die Epilepsiechirurgie in den letzten Jahren revolutioniert. Die funktionelle Magnetresonanztomographie (fMRT) wird zusehends zur Lokalisation des primären motorischen, des somatosensorischen Kortex sowie zur Lateralisation und Lokalisation von Sprach- und Gedächtnisfunktionen eingesetzt. Rezente Studien sind vielversprechend, dass die fMRT dazu beitragen kann, das individuelle Risiko für postoperative Sprach- und Gedächtnisdefizite näher bestimmen zu können.

Zusammen mit anderen strukturellen und funktionellen bildgebenden Verfahren kann die fMRT entscheidend zu einer weiteren Verbesserung des postoperativen Outcomes nach epilepsiechirurgischen Eingriffen beitragen, indem die epileptogene Zone, die entfernt werden muss, und der eloquente Kortex, der erhalten bleiben soll, besser definiert werden können.

Schlüsselwörter: Epilepsiechirurgie, funktionelle Bildgebung, Sprache, episodisches Gedächtnis, Lateralisation, Hemisphärendominanz, Lokalisation, anteriore Temporallappenresektion

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Abbreviations

AED = antiepileptic drugs
ATLR = anterior temporal lobe resection
BOLD = blood oxygen level dependent
DTI = diffusion tensor imaging
EPI = echo planar imaging
ESM = electro-cortical stimulation mapping
fMRI = functional magnet resonance imaging
HC = hippocampus
IAP = intracarotid amobarbital procedure
IFG = inferior frontal gyrus
MFG = middle frontal gyrus
MTL = medial temporal lobe
SFG = superior frontal gyrus
SMG = supramarginal gyrus
STG = superior temporal gyrus
TLE = temporal lobe epilepsy
VBM = voxel-based morphometry

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Background

Seizure freedom is the major aim of epilepsy treatment. Cognitive impairment is a frequent comorbidity in focal epilepsies and has a major impact on quality of life. Cognitive deficits can either result from the underlying disease as a consequence of seizures or interictal epileptic activity, or can be caused by adverse effects of antiepileptic drugs (AED) [1].

In temporal lobe epilepsy (TLE), particularly memory impairment and naming difficulties have been reported [2, 3]. These can already be observed in some patients with a recent onset of epilepsy [4], which supports the hypothesis that cognitive problems cannot fully be explained by adverse effects of medication. Patients who are refractory to AED treatment are at higher risk of suffering from cognitive impairment.

In patients with medically refractory TLE anterior temporal lobe resection (ATLR) is an effective and safe treatment option, leading to seizure freedom in up to 60-70% of these patients [5, 6]. Prior to surgery, comprehensive pre-surgical assessment is conducted which aims at identifying the epileptic brain tissue that has to be removed for the patient to become seizure free [7]. At the same time neuropsychological deficits such as language and memory impairment have to be avoided.

In recent years, epilepsy surgery is carried out earlier in the course of the disease, and the potential benefits must be carefully weighed against the potential risks of decline. For this, eloquent brain areas have to be identified which must be spared from the resection. Functional MRI (fMRI) has proven a valid and reliable tool to investigate cognitive functions non-invasively during pre-surgical assessment. Over recent years it has increasingly replaced invasive procedures such as the WADA-test as it is cheaper, non-invasive and repeatable. Compared to baseline neuropsychological assessment it further has the potential of providing additional information regarding lateralisation and localisation of language and memory function and particularly allows evaluation of functional reorganisation processes.

ATLR carries the risk of language and memory decline, e.g. verbal memory and naming decline after surgery within the language-dominant, usually left hemisphere [2]. Language fMRI is well established in many centres and is often applied to identify the language dominant hemisphere on an individual level. However, the localisation of language areas is much more complicated and still requires invasive electro-cortical stimulation mapping (ESM). Regarding memory function, recent studies were promising that memory fMRI has a great potential to predict postoperative memory decline after surgery even in individual patients, which is one of the ultimate goals of clinical neuroimaging.

Methodological Considerations

As discussed above invasive methods have been routinely used to identify the eloquent cortex in the past: the Wada-Test (intracarotid amobarbital procedure, IAP) was widely used to *lateralise* function, and ESM is still the gold standard to *localise* eloquent cortex. Over the last decades, non-invasive methods, predominantly fMRI have been established for this purpose [8, 9]. Obvious advantages of non-invasive methods are their low risks and less strain for the patient. They can be applied in healthy volunteers for research purposes allowing systematic comparison of different study groups.

Functional MRI, like most other non-invasive imaging tools, is an activation based method. The rationale behind this is that if a certain cognitive function is used, relevant brain areas will be activated. Blood flow will increase in these areas to compensate for the higher demand of oxygen. In fMRI, this is displayed by the BOLD (blood-oxygen-level-dependent) contrast which represents the regional changes in blood flow over time. To be able to get a reasonable temporal resolution echo planar imaging (EPI), a fast MRI sequence, is used. Functional MRI has a high spatial resolution which, in principal, allows very good localisation of areas in the brain that are involved in certain tasks. However, which areas will be activated depends on the fMRI paradigm.

It is important to assure sufficient task performance as only then activation can be accurately interpreted in relation to function. This needs to be considered in fMRI paradigm design, especially when applying fMRI to patient groups in which cognitive performance can vary considerably. It is mandatory to make sure that participants understand and follow task instructions. However, during fMRI the subject's performance cannot easily be assessed. The majority of fMRI paradigms applied to date use covert tasks (e.g. thinking of words, but not speaking out loud) or assess performance with a joy-stick or button press response. This can restrict the variety of possible responses that can be used in an fMRI paradigm. More recently developed devices such as MRI-compatible microphones can now be used to monitor speech during fMRI. For simple paradigms which only require basic analysis, e.g. as used for clinical language fMRI, scanner implemented software for online data analysis can be employed to show activation patterns during the scan.

In epilepsy, seizures and interictal epileptic activity as well as AEDs may alter fMRI results [10].

Most cognitive tasks do not only rely on one particular function. If visual stimuli are presented, activation of visual cortex can be expected. If the subject is asked for a motor response, motor activation can be expected. To differentiate between activation related to a certain function and other activation, neuroanatomical information (e.g. Broca's area, Wernicke's area for language; medial temporal lobe structures for memory) may be used to interpret results. Further, most fMRI paradigms include other tasks with the aim to control for irrelevant activations; only activation in the "real" task that exceeds activations during the control task is considered.

What brain areas will be displayed as "active" varies substantially with different statistical thresholds which can be applied to the data. A high threshold reduces the sensitivity in detecting activations as well as the extent of activation clusters while a low threshold increases the risk of false-positive activations.

In summary caution is needed in the interpretation of the results. Firstly, areas activated by a particular fMRI paradigm are not necessarily essential for performing a task. Secondly, not necessarily all areas involved in a task will be activated by one particular fMRI paradigm and finally extent and magnitude of activation seen in a task does not necessarily relate to the competence with which the task is performed. One must also bear in mind the limitation of fMRI techniques especially in the temporal lobes, such as lower MRI signal to noise ratio due to susceptibility artefacts and signal loss in areas that are close to larger blood vessels and bone tissue.

Language

During evaluation for epilepsy surgery, fMRI is the most frequently applied non-invasive method for language imaging [9]. Clinically applied paradigms focus on the classic language areas such as Broca's area (IFG) and Wernicke's area (SMG, STG). Covert lexical word generation (i.e. thinking of words starting with a given letter) is an expressive language task that reliably activates the IFG (**Figure 1**). Posterior temporal lobe (TL) activation (SMG, STG) can be achieved by more receptive tasks, e.g. semantic decision tasks (i.e. which word does not match the others: shirt, gloves, shoes, rose?) or story listening tasks. Numerous language paradigms have been applied in group studies which may partly explain some differences in the results between studies [9, 11]. Studies comparing language fMRI with the classic invasive methods (Wada-Test, ESM) showed that fMRI is a valid method for identifying the language dominant hemisphere [11 - 13]. Functional MRI seems more likely to elicit bilateral language representation compared to the Wada-Test; however, the meaning of this finding for language function after surgery is not fully understood [13]. Accurate localisation of language areas with fMRI is not yet established. First of all, test-retest series have shown that the localisation of areas that were

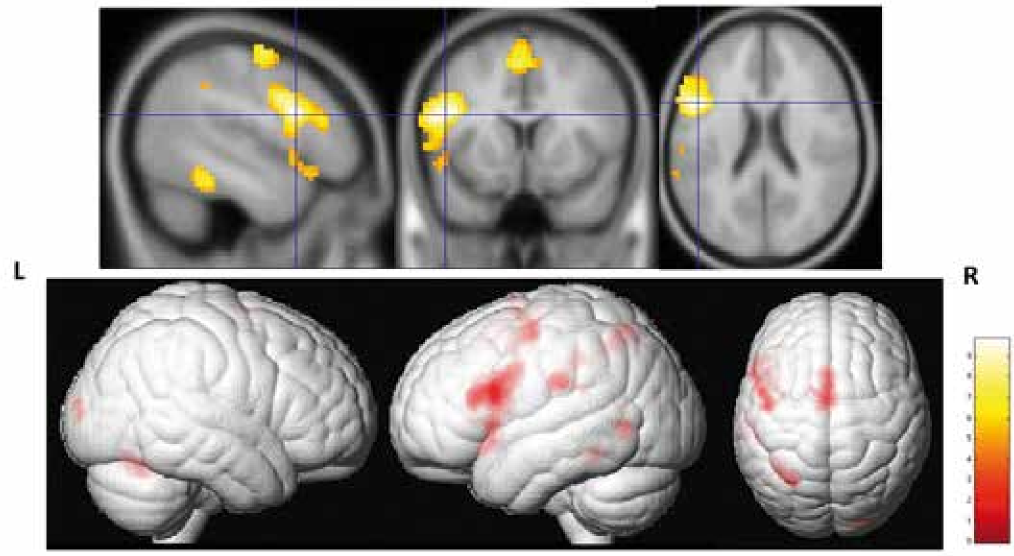

Figure 1: Language fMRI activations during covert lexical fluency in a single subject at p = .05, family wise error; strong activation can be seen in the left IFG, as well as in the left MFG and SFG.

activated during a specific language fMRI task was less reliable than lateralisation [14]. Furthermore, ESM studies showed only imperfect overlap with activation clusters of fMRI: in some cases electric stimulation of fMRI activated brain areas did not result in language disturbances [15], while in others crucial areas were not displayed during fMRI [16]. The differences may be related either to the applied language paradigms or the statistical thresholds. To date, language fMRI localisation is not suitable for resection decision [17] but may be helpful in planning electrode placement for ESM [8].

Aphasia is rare after temporal lobe surgery. More subtle language decline such as word finding difficulties have been reported in up to 50% of patients after ATLR of the language dominant hemisphere. In left TLE, a predictive value of fMRI language lateralisation for naming decline [18] as well as for verbal memory [19, 20] could be shown. However, prediction models on an individual level are not yet sufficient to be applied in clinical routine. Future studies will need to investigate whether specific naming paradigms will allow more accurate prediction in individual patients. Apart from presurgical evaluation, language fMRI has also be applied in other epilepsy syndromes. As an example, in primary reading epilepsy, a study combining EEG and fMRI showed specific regions that were involved in seizure generation during reading [21]. Brain activation patterns can be assessed repeatedly during language development in certain epilepsies which may provide prognostic information of potential language achievement in relation to seizures and help finding new rehabilitation strategies [21, 22].

Memory

The occurrence of material specific (verbal and visual) memory impairment after ATLR indicates major relevance of these areas for successful memory function. Intracranial electrophysiological recordings during verbal encoding tasks have shown greater responses in anterior hippocampal and parahippocampal regions for words remembered than those forgotten [23]. At first, these results could not be replicated with functional imaging studies, with many showing encoding related activations in posterior hippocampal and parahippocampal regions, which would be left intact following ATLRs. One possible explanation for this apparent conflict is that anterior temporal regions are subject to signal loss during fMRI sequences, which is most prominent in the inferior frontal and inferior lateral temporal regions [24]. The anatomical position of the hippocampus which rises from anterior to posterior may explain greater susceptibility-induced signal loss in the anterior (inferior) relative to the posterior (superior) hippocampus which may have been one reason for the relative lack of anterior hippocampal activation in early fMRI studies of memory. Another reason for the lack of activation in the anterior medial temporal lobe (MTL) may be that most previous memory fMRI studies employed blocked experimental designs which have the advantage that they are generally most efficient in detecting differences between two conditions. However, the interpretation of their contrasts remains problematic assuming that the effects shown by these contrasts reflect differences in memory encoding, rather than any other differences between the two conditions. This approach does not account for subsequent memory effects (i.e. which stimuli were encoded successfully). More recent studies applied event-related designs which have the big advantage that brain regions showing greater activation during encoding of different (material specific) items that were subsequently remembered compared to items that were subsequently forgotten can be identified, representing the neural correlates of memory encoding [25].

A previous study compared results from a blocked and event-related analysis of memory fMRI of words, pictures and faces: Only the event-related analysis of successfully encoded stimuli showed significant activations in the anterior MTL whereas simply viewing the different stimuli (using a blocked analysis without taking into account whether items were subsequently remembered or not) revealed predominant activation in the posterior hippocampus [26]. Therefore this study provided evidence for a functional dissociation between anterior and posterior hippocampal regions.

In summary, although event-related designs are less powerful than block designs at detecting differences in two different brain stages and also more vulnerable to alterations in the hemodynamic response function, they have the big advantage of permitting specifically the detection of subsequent memory effects due to successful encoding.

Lateralisation and Localisation of Memory Function

Patients with unilateral TLE often present with memory impairment which is specific to certain materials (e. g. verbal and visual). After temporal lobe surgery of the language dominant hemisphere more often verbal memory decline can be observed [27] while TL surgery in the non-dominant hemisphere is more likely to result in visual-spatial memory decline [28]. Many fMRI studies demonstrated material-specific lateralisation of memory function in prefrontal but also medial-temporal regions [26, 29, 30]. For clinical purposes, usually paradigms are applied that show bilateral MTL activation in healthy controls [31 - 33]. Previous fMRI studies in patients reported reduced activation in the TL ipsilateral to the seizure onset [29, 30, 34, 35]. These results were comparable with the Wada-Test [30]. As mentioned above, most of these studies employed block designs and showed more posterior HC activations. More recent studies using event-related analyses showed material-specific lateralisation of memory function in more anterior hippocampal regions during successful memory encoding [26] and therefore in an area which is most likely to be resected during standard ATLR. The reduced activation within the affected TL but increased contralateral MTL activation during memory fMRI has provided further evidence of reorganisation of memory function in TLE [31, 33, 35]. Still, it is a matter of debate if reorganisation towards the healthy hemisphere is effective, and whether it may be protective for memory decline after surgery. By correlation of fMRI activation and performance on standard neuropsychological memory tests it has been shown that higher MTL activation ipsilateral to the pathology was associated with better memory performance while contralateral, compensatory activation correlated with poorer performance [31, 33]. In one study that investigated patients with left and right TLE, higher MTL activation was observed in the healthy TL. However, better verbal memory was still related to left MTL activation [36]. This explains why good verbal memory is a risk factor for postoperative decline [37, 38].

Prediction of Memory Decline

Two different models of hippocampal function have been proposed to explain memory deficits following unilateral ATLR, the hippocampal reserve model and the functional adequacy theory [39]. According to the hippocampal reserve model, postoperative memory decline depends on the capacity or reserve of the contralateral hippocampus to support memory following surgery, while the functional adequacy model suggests that it is the capacity of the hippocampus that is to be resected that determines whether changes in memory function will be observed. Over the last years many studies focused on the identification of prognostic indicators for risk of memory loss after ATLR. The severity of hippocampal sclerosis (HS) on MRI turned out to be an important predictor, being inversely correlated with a decline in verbal memory following left ATLR, with less severe HS increasing the risk of memory decline [40]. Another recognised prognostic factor for memory decline after ATLR was preoperative performance on neuropsychological tests, with higher preoperative scores indicating a greater risk for postoperative decline [37, 38, 41 - 43]. Language lateralisation assessed by the IAP or more recently language fMRI has been found helpful to predict memory outcome [43 - 47]. These risk factors reflect the functional integrity of the resected temporal lobe and suggest that patients with residual memory function in the pathological hippocampus are at greater risk of memory impairment after ATLR. Other epilepsy related factors such as age of epilepsy onset and duration of epilepsy have also been identified as useful predictors of postoperative outcome [48].

Recently, memory fMRI has also been shown to be a potential predictor of postoperative memory decline after ATLR. Several studies have investigated the predictive value of fMRI for verbal memory decline [45, 49 - 51]. Only a few fMRI studies have investigated visual memory after ATLR [34, 47, 51]. In patients with left HS, greater verbal memory encoding activity in the left hippocampus prior to surgery predicted the extent of verbal memory decline following left ATLR [35, 49 - 51]. These findings have since been replicated and extended to patients undergoing right ATLR [31, 51]. Other groups employed asymmetry-indices to account

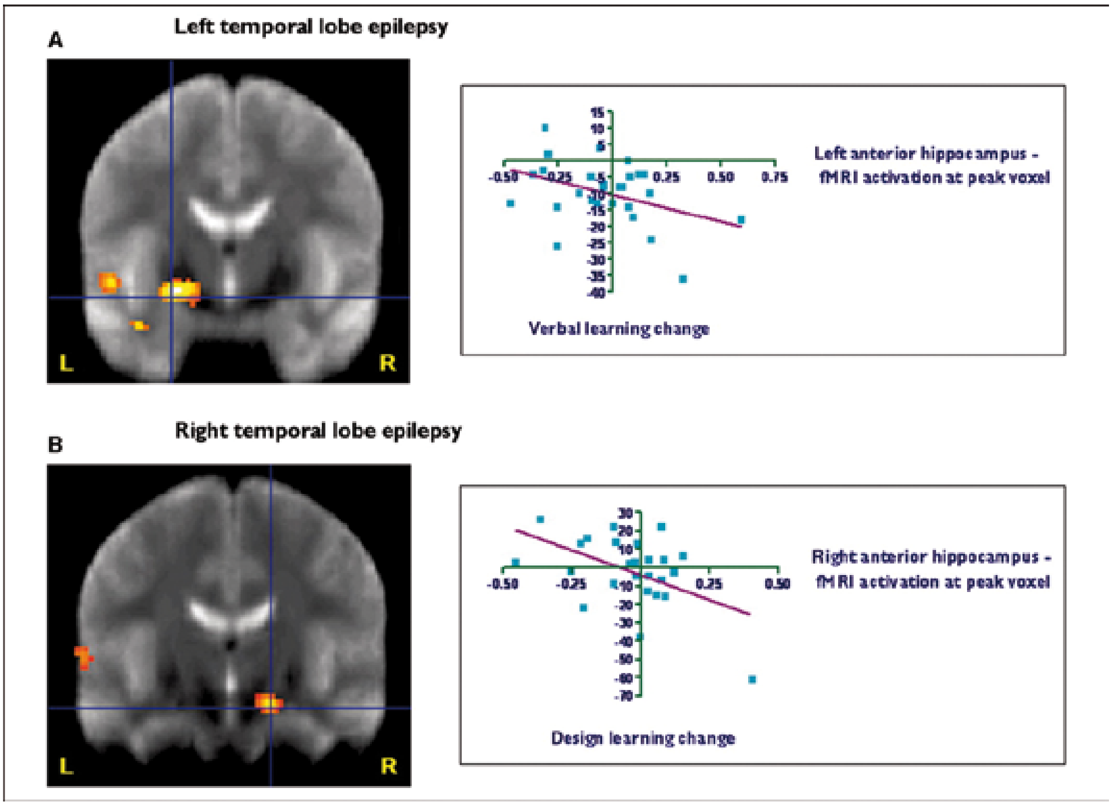

Figure 2: (adapted from Bonelli et al., Brain 2010): Functional MRI and prediction of postoperative verbal and visual memory decline
A: Patients with left temporal lobe epilepsy. Greater left anterior hippocampal activation for successful verbal encoding correlates with greater verbal memory decline after left anterior temporal lobe resection.
B: Patients with right temporal lobe resection. Greater right anterior hippocampal activation for successful encoding of faces correlates with greater visual memory decline after right anterior temporal lobe resection. The correlations for the peak voxel are illustrated on the right.

for contralateral hippocampal activation and demonstrated that relatively higher activation in the ipsilateral HC was associated with greater memory decline [34, 47]. Using a material-specific memory encoding paradigm in a large cohort of patients with unilateral TLE, Bonelli et al. demonstrated that relatively greater ipsilateral anterior MTL activation was predictive of verbal and visual memory decline after left or right ATLR while relatively greater posterior MTL activation was associated with better verbal and visual memory outcome [31] (**Figure 2**). In this study memory asymmetry indices of anterior MTL activation had the strongest predictive value for verbal and visual memory decline compared to other epilepsy related variables. A prediction model comprising the aforementioned memory asymmetry index in combination with degree of language dominance and preoperative verbal memory performance correctly predicted verbal memory decline in all patients of the study. Prediction of visual memory decline was less accurate [31].

Future Perspectives

As fMRI is a non-invasive tool the effects of epilepsy surgery on the brain and factors that are associated with effective functional reorganisation after surgery can be studied with repeated fMRI [18, 21, 52]. Further, newer structural MRI techniques and analyses have been used to infer on functional organisation of the brain. A voxel-based morphometry (VBM) study demonstrated a strong association of lateralisation of white matter in parts of the frontal and temporal lobes with individual language dominance [20]. A DTI study showed a predictive value of the laterality of fronto-temporal tract integrity for postoperative naming decline [53]. In case functional MRI cannot be applied due to a patient's low capacity, these techniques may provide useful information. Further, the combination of the different structural MRI methods with fMRI may substantially improve prediction of the effects of surgery on cognitive function.

Functional connectivity can elicit neuronal networks that contribute to various cognitive tasks. It has been shown that cognitive impairment is often accompanied by reduced functional connectivity. Whether these methods may add to the prediction of post-operative cognitive outcome remains a topic of current research [54, 55].

Conclusions

Functional MRI is increasingly used to image cognitive function such as language and memory function. In the pre-surgical evaluation it can reliably assess language dominance and it helps to predict risks of cognitive decline after surgery. Up to date, invasive methods have not been fully replaced but non-invasive techniques may help planning invasive procedures. Non-invasive methods allow us to investigate healthy volunteers and to systematically compare different study groups and changes in activation over time to assess mechanisms of cognitive development and functional reorganisation. This may help to improve the individual prognosis of even subtle cognitive deficits and may stimulate the development of new therapeutic strategies for cognitive rehabilitation.

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