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Summary

Functional MRI (fMRI) is increasingly utilized as a non-invasive alternative to cortical mapping and Wada test during the last two decades in patients with medically refractory epilepsy who are candidates for epilepsy surgery. fMRI acquired a crucial role in everyday clinical routine in determining important brain functions such as motor, language or memory. Mapping motor function by fMRI is particularly useful when anatomic structures are distorted by mass effects or dysplastic lesions making it difficult to ascertain the location of the central sulcus with certainty. fMRI studies comparing language lateralization in right-handed normal adults with epilepsy patients, observed that patients with epilepsy had a higher incidence of atypical language dominance, which was particularly true for patients with left sided seizure foci. Preoperative language fMRI could be used to stratify patients in terms of risk for language decline after epilepsy surgery. In memory fMRI, hippocampus has been notoriously difficult to activate reliably. This may be at least partly attributable to difficulties in disengaging memory function for a control condition. The hippocampus is also in a region of comparatively high static susceptibility, resulting in decreased sensitivity for fMRI signal. Nevertheless, memory fMRI in presurgical assessment provides valuable information.

Although fMRI results increasingly influence diagnostic and therapeutic decision making in epilepsy surgery, there are still numerous problems yet to be solved.

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Key words: fMRI, imaging, epilepsy surgery, language, memory, motor function

Zur klinischen Bedeutung der funktionellen Kernspintomographie (fMRI) in der Epileptologie

fMRI-Untersuchungen werden in den letzten zwei Jahrzehnten zunehmend als eine Alternative zu invasiven Verfahren, wie Wada-Test und kortikale Stimulation, in der präoperativen Diagnostik von epilepsiechirurgischen Kandidaten eingesetzt. Die Bedeutung des fMRIs für die Klinik liegt in der Identifizierung wichtiger Hirnfunktionen wie der Motorik, der Sprache und des Gedächtnisses. Dabei zeigt sich die Lokalisation mittels fMRI besonders hilfreich bei der Bestimmung des Sulcus centralis, wenn Massenläsionen oder ausgedehnte Missbildungen eine anatomische Bestimmung erschweren. Die Bestimmung der hemisphärischen Sprachdominanz mittels fMRI erlaubt es heute, diejenigen Patienten vor einem epilepsiechirurgischen Eingriff zu identifizieren, die ein erhöhtes Risiko möglicher sprachlicher Einbussen infolge einer Resektion im Bereich der sprachdominanten Hemisphäre eingehen. Das fMRI des Hippokampus und seiner Gedächtnisfunktionen ist ein schwieriges Unterfangen, da Gedächtnisbildungsprozesse nur in engen Grenzen experimentell kontrollier- und steuerbar sind. Zudem bestehen methodische Herausforderungen, da die hippokampale Formation aufgrund vermehrter Suszeptibilitätsartefakte geringe Signalausbeuten liefert. Einerseits beeinflussen Ergebnisse aus fMRI-Untersuchungen heute bereits vermehrt therapeutische Entscheidungen in der Epilepsiechirurgie andererseits bestehen nach wie vor wichtige ungelöste methodische Probleme, die eine grosse Herausforderung für die Methodenforschung darstellen.

Schlüsselwörter: fMRI, Bildgebung, Epilepsiechirurgie, Sprache, Gedächtnis, Motorik

De l'importance clinique de la tomographie à spin nucléaire (IRMf) dans l'épileptologie

Depuis deux décennies, l'option IRMf remplace de plus en plus les procédés invasifs d'investigation tels que le test de Wada et la stimulation corticale dans le diagnostic préopératoire de candidats à la chirurgie épileptique. L'intérêt clinique de l'IRMf consiste dans le fait qu'elle permet d'identifier des fonctions cérébrales importantes telles que la motricité, la langue et la mémoire. La localisation au moyen de l'IRMf est particulièrement utile pour la détermination du sillon central lorsque des lésions massives ou des malformations étendues compliquent une détermination anatomique. La détermination du siège hémisphérique de la dominance linguistique permet aujourd'hui d'identifier avant une intervention chirurgicale ceux parmi les patients épileptiques qui encourent un plus grand risque de pertes linguistiques en raison d'une résection dans le domaine de l'hémisphère où siège la dominance linguistique. L'IRMf de l'hippocampe et de ses fonctions mnésiques est une procédure difficile car les possibilités de contrôle et de commande expérimentale des facultés mnésiques restent très limitées. Les défis sont aussi d'ordre méthodologique, car la formation hippocampique fournit une faible moisson signalétique en raison de multiples susceptibilités artificielles. D'un côté, les résultats d'examens IRMf influencent déjà de plus en plus les décisions thérapeutiques dans la chirurgie épileptique, de l'autre côté, il reste des problèmes méthodologiques importants à apréhender qui posent de grands défis à la recherche méthodologique.

Mots-clés : IRMf, imagerie, chirurgie de l'épilepsie, langage, mémoire, motricité

Functional magnetic resonance imaging

Functional neuroimaging maps the activity of the living brain in space and time. Magnetoencephalography and electroencephalography offer direct measurements of neural activity with high temporal resolution but are limited by difficulties in defining the spatial location and extent of activation. Neuroimaging methods based on metabolic and vascular parameters, while offering limited temporal resolution, provide excellent spatial resolution and localization of brain function. Functional magnetic resonance imaging (fMRI), enables completely noninvasive imaging of changes in blood oxygenation and perfusion. Unlike positron emission tomography (PET), fMRI does not require exposure to ionizing radiation. Compared to PET, fMRI provides superior temporal and spatial resolution and increased sensitivity for detecting task activation in individual subjects through signal averaging. On the other hand, PET provides a greater repertoire of image contrast sources. Whereas fMRI is primarily sensitive to hemodynamic changes, PET images can reflect blood flow, glucose utilization, oxygen consumption, and receptor binding. PET also provides a silent environment that is not affected by electromagnetic interference or the presence of ferrous objects. However, PET scanning is less widely available and significantly more costly than fMRI because of the need for on-line tracer synthesis.

The primary contrast phenomena for fMRI is blood-oxygenation-level-dependent (BOLD) contrast. BOLD reflects a complex interaction between blood flow, blood volume, and hemoglobin oxygenation [1 - 3]. Functional contrast is obtained because the iron present in hemoglobin becomes paramagnetic only when it is deoxygenated producing a local susceptibility increase manifested as a change in T2* images [4]. This change in hemoglobin oxygenation can be observed using a variety of pulse sequences, including routine gradient-echo sequences and gradient-echo echoplanar sequences, which particularly emphasize T2* effects [4].

Task-specific BOLD signal changes are not directly quantifiable in physiologic units and instead are expressed as a percentage signal change or as a statistical significance level based on a particular statistical model. Absolute or resting function cannot be easily assessed, and for clinical studies it may be difficult to know whether any observed abnormalities are due to baseline or task-specific effects. A typical BOLD response consists of a 0.5-5% change in regional image intensity that develops over 2-8 seconds following task initiation, typically with an initial peak or overshoot, a somewhat lower plateau for sustained tasks, and often an undershoot of the baseline following task completion. The peak latency of several seconds represents a major limiting factor in the temporal resolution of functional imaging methods.

Preoperative mapping of sensorimotor cortex

A large number of fMRI studies have demonstrated primary sensorimotor cortex activation along the central sulcus during movement, including demonstration of the somatotopic organization of this region [5 - 7]. Movement not only engages motor cortex but also provides tactile and proprioceptive sensory input, so activation is not confined to the motor cortex (anterior bank of the central sulcus) but rather involves primary motor and sensory areas [8]. Finger movements are used most commonly, since face or proximal limb movements increase the likelihood of unacceptable movement artifacts. The magnitude of activation in primary motor cortex is directly dependent on the rate of finger movement [9]. Complex, sequential movements of individual digits produce additional activation in associated regions such as premotor cortex, supplementary motor area, and postcentral sulcus bilaterally [10].

The clinical utility of such maps is in functional localization prior to surgery in this region for tumor or seizure focus resection. When the lesion is in close proximity to primary sensorimotor cortex along the central sulcus, precise localization of the activated region relative to the lesion could potentially help predict whether a sensorimotor deficit is likely to occur from lesion resection. It might also be possible to minimize any resulting deficit by purposefully sparing activated and immediately surrounding regions, although no quantitative studies have verified the effectiveness of such an approach. fMRI information is perhaps particularly useful when anatomic structures are distorted by mass effects or dysplastic lesions making it difficult to ascertain the location of the central sulcus with certainty (**Figure 1**). Motor cortex localization with fMRI has generally been highly concordant with intraoperative electrocortical stimulation mapping [11, 12]. widely used language paradigms compared to listening, repeating, reading. Subjects are given a beginning letter, a semantic category, or a word, and must retrieve a phonologically or semantically associated word. This

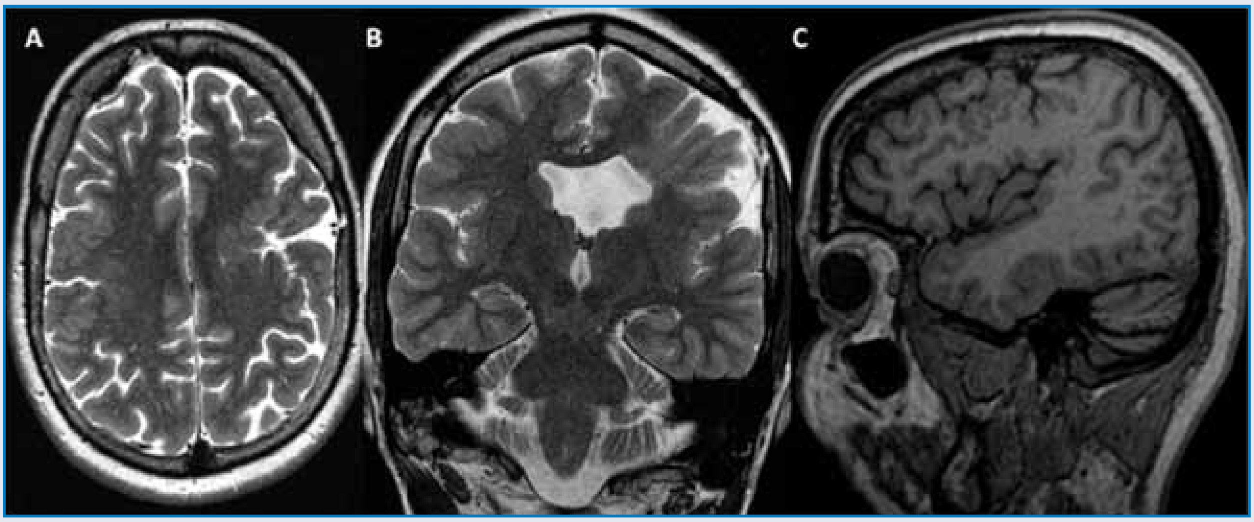

Figure 1a: Mapping motor function in a patient with epilepsy and bilateral pericentral polymicrogyria.

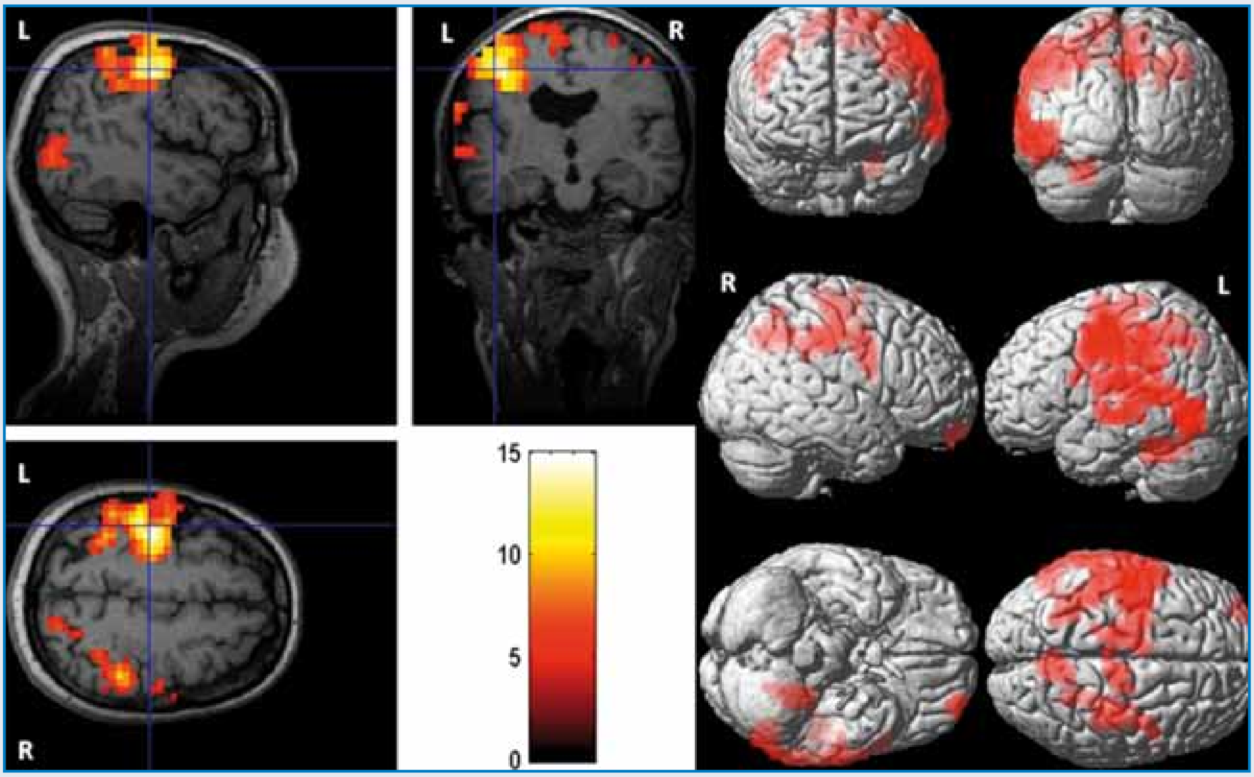

Figure 1b: Bilateral pericentral polymicrogyria: A – axial T2-weighted; B – coronal T2-weighted and C – sagittal T1-weighted images show bilateral polymicrogyria in pericentral area with schizencephalic cleft.

Preoperative mapping of language systems

The aim of localizing language functions preoperatively is to minimize postoperative language deficits that can result from epilepsy surgery [13]. 'Word generation' tasks (also called fluency tasks) that require word retrieval in response to a verbal cue are most task strongly activates the dominant inferior and dorsolateral frontal lobe, including prefrontal and premotor areas. Posterior language areas such as middle and inferior temporal gyri, fusiform gyrus, and angular gyrus are only weakly activated by the word generation task compared to a resting state or a word reading control [14 - 16].

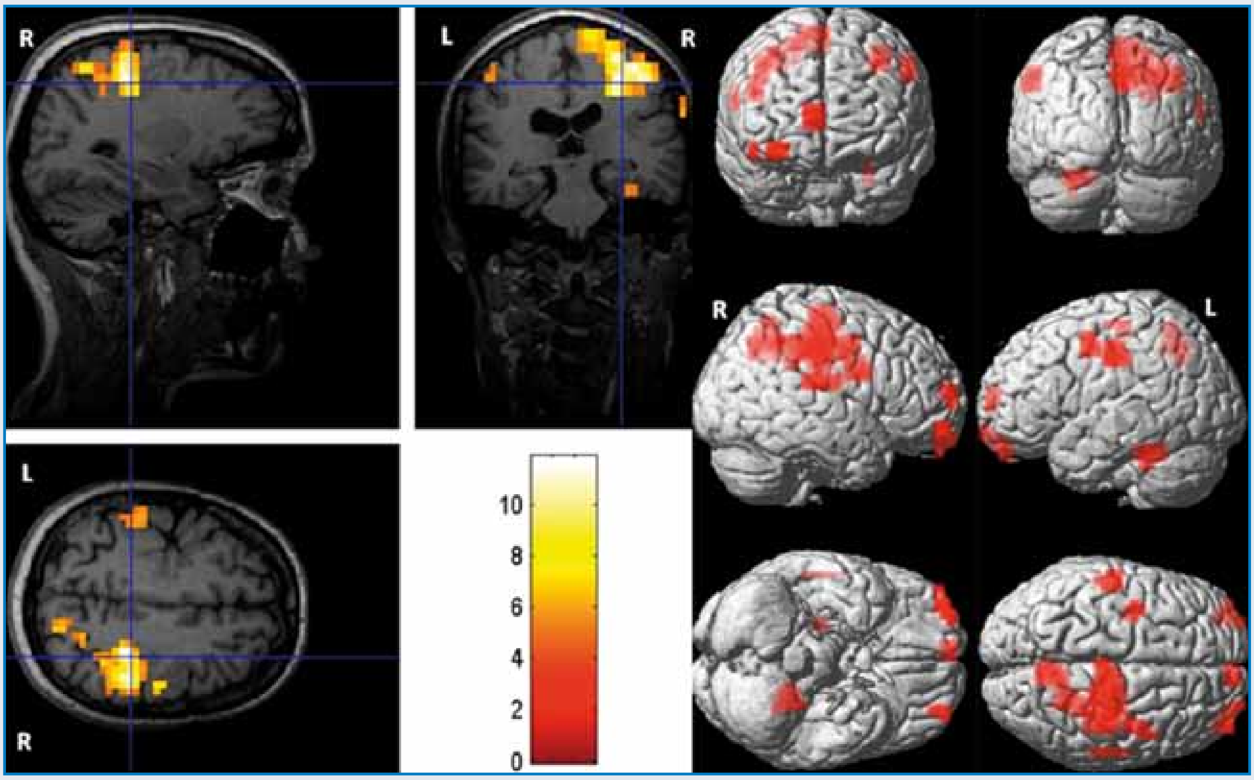

Figure 1c: Finger-to-thumb opposition task performed on the right; BOLD signal is registered bilaterally in primary motor cortex (left > right). R – right, L – left.

fMRI studies comparing language lateralization in right-handed normal adults with epilepsy patients, observed that patients with epilepsy had a higher incidence of atypical (symmetric or right-lateralized) language dominance, which was particularly true for patients with left sided seizure foci [17, 18] (**Figure 2**). In one study there was a clear relationship between lateralization index and age of onset of seizures, with language tending to shift more toward the right hemisphere with earlier onset [19]. These observations are in agreement with Wada studies showing effects of side of seizure focus and age at onset on language lateralization [20].

Wada test comparisons

There is a certain level of agreement between fMRI and Wada tests on measures of language lateralization [21 - 23]. fMRI offers a valid alternative to invasive Wada test for establishing language dominance, and it is likely that it will also replace the Wada test for assessing presurgical memory function in the nearer future. Some results are, however, conflicting due to differences in paradigms and analysis procedure [24]. Most of the studies, however, involved relatively small sample sizes (7-20 patients) and relatively few crossed-dominant individuals. The recent study on 60 patients with temporal lobe epilepsy aimed to determine whether preoperative language mapping using fMRI is useful for predicting which patients are likely to experience verbal memory decline after left-sided anterior temporal lobe resection [14]. Preoperative language mapping with fMRI was compared with preoperative Wada testing for language and memory lateralization. Verbal memory decline occurred in over 30% of patients. Good preoperative performance, late age at onset of epilepsy, left dominance on fMRI, and left dominance on the Wada test were each predictive of memory decline. Preoperative performance and age at onset together accounted for roughly 50% of the variance in memory outcome ($p < 0.001$), and fMRI explained an additional 10% of this variance (p </= 0.003). Neither Wada memory asymmetry nor Wada language asymmetry added additional predictive power beyond these noninvasive measures. It was suggested that preoperative fMRI is useful for identifying patients at high risk for verbal memory decline prior to left-sided anterior temporal lobe resection. Lateralization of language is correlated with lateralization of verbal memory, whereas Wada memory testing is either insufficiently reliable or insufficiently material-specific to accurately localize verbal memory processes.

Comparisons with cortical stimulation mapping

A number of studies have compared fMRI motor and language maps with the corresponding maps obtained using cortical stimulation mapping [11, 22, 25]. These studies are of great potential interest because they permit a test of whether fMRI activation foci represent 'critical' language areas. The assumption underlying the cortical stimulation technique is that the temporary deactivation induced by electrical interference will identify any such critical areas. The reports comparing fMRI and cortical stimulation have encouraging results, although they involved relatively small samples (<15 patients). Methods for comparing the activation maps have tended to be qualitative and subjective rather than quantitative and objective, with a few exceptions [26, 22].

across subjects. Several factors make these comparisons particularly difficult to carry out. One problem is in matching the task characteristics across the two modalities. fMRI studies usually employ controls for nonlinguistic aspects of task performance, whereas this is typically not true of stimulation mapping studies. For example, stimulation studies often focus on speech arrest, which can result from disruption of motor or attentional systems as well as language systems [28]. A second difficulty is the fact that many fMRI activation foci lay buried in the depths of sulci, which are not available for stimulation mapping. Thus, it is reason-

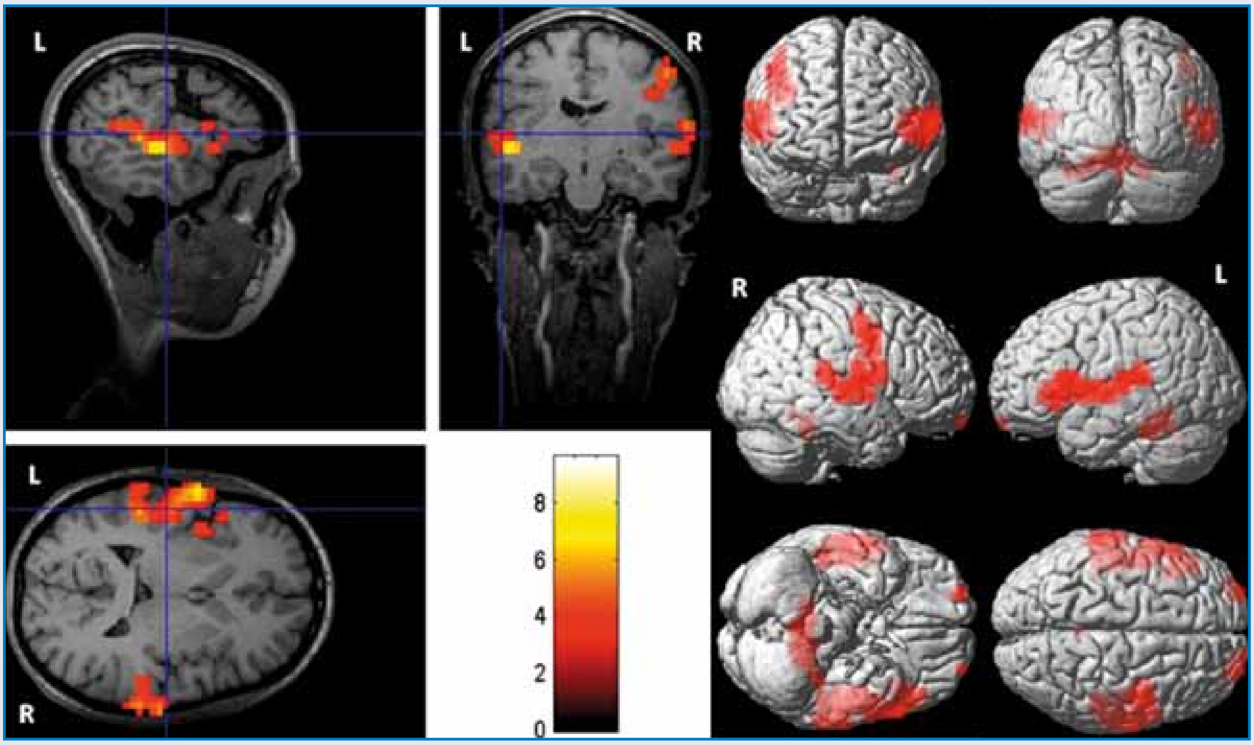

Figure 2: Mapping language in a patient with epilepsy and bilateral pericentral polymicrogyria. Word generation task; BOLD signal is seen bilaterally in Wernicke's area and on the left in Broca's area (predominantly left-sided activation). R – right, L – left.

In 14 patients, poor sensitivity of fMRI was observed for the naming and verb generation tasks (22 and 36%, respectively) in frontal and temporo-parietal areas. The specificity of fMRI was good in all conditions (97% for the naming task and 98% for the verb generation task). Better correlation (sensitivity, 59%; specificity, 97%) was achieved by combining the two fMRI tasks. Variation of the analysis threshold to $P < 0.05$ increased the sensitivity to 66% while decreasing the specificity to 91%. Postoperative fMRI data (for the cortical brain areas studied intraoperatively) were in accordance with brain mapping results for six of eight patients. Complete agreement between pre- and postoperative fMRI studies and direct brain mapping results was observed for only three of eight patients [27].

Sensitivity and specificity were highly variable able to expect that many foci of activation observed by fMRI simply will not be tested adequately during cortical stimulation mapping.

Prediction of language outcome

A more meaningful measure of the validity of fMRI language maps, rather than comparison with Wada test or cortical stimulation mapping, is how well they predict postoperative language deficits. The ability of preoperative fMRI to predict naming decline was assessed in 24 consecutive patients undergoing left anterior temporal lobectomy (ATL) [29]. fMRI employed a semantic decision versus sensory discrimination protocol. All left ATL patients also underwent Wada testing and intraoperative cortical stimulation mapping, and surgeries were performed blind to the fMRI data. Compared to a control group of 32 right ATL patients, the left ATL group declined postoperatively on the 60-item Boston Naming Test ($p < 0.001$). Within the left ATL group, however, there was considerable variability; with 13 patients (54%) showing significant declines relative to the control group and the remainder showing no decline. Language laterality index based on fMRI activation in a temporal lobe region of interest was strongly correlated with outcome ($r = -0.64$, $p < 0.001$), such that the degree of language lateralization toward the surgical (left) hemisphere was related to poorer naming outcome, whereas language lateralization toward the nonsurgical (right) hemisphere was associated with less or no decline. The fMRI temporal lobe language laterality index showed 100% sensitivity, 73% specificity, and a positive predictive value of 81% for predicting significant decline. By comparison, the Wada language laterality index showed a somewhat weaker correlation with decline ($r = -0.50$, $p < 0.05$), 92% sensitivity, 43% specificity and a positive predictive value of 61%. These results suggest that preoperative fMRI could be used to stratify patients in terms of risk for language decline. It is crucial to note, however, that these results hold only for the particular methods used in the study and may not generalize to other fMRI protocols, analysis methods, patient populations, or surgical procedures.

The role of fMRI in planning epilepsy surgery

Although fMRI results increasingly influence diagnostic and therapeutic decision making in epilepsy surgery [30], it remains to be established how useful fMRI language activation maps will be for more precise planning of surgical resections. There are though some significant problems:

- inconsistencies in language maps produced by different activation protocols
- the failure to date to find an activation protocol that reliably activates the anterior temporal lobe, where the majority of epilepsy surgeries are performed
- an inadequate understanding of the specificity of fMRI activations. Thus, those who would use fMRI activation maps to decide which brain regions can be resected in an individual patient run two risks:
- resection of critical language zones that are 'not activated' because of insensitivity of the particular language activation protocol employed, resulting in postoperative language decline
- sparing of 'activated' regions that are actually not critical for language, resulting in suboptimal seizure control.

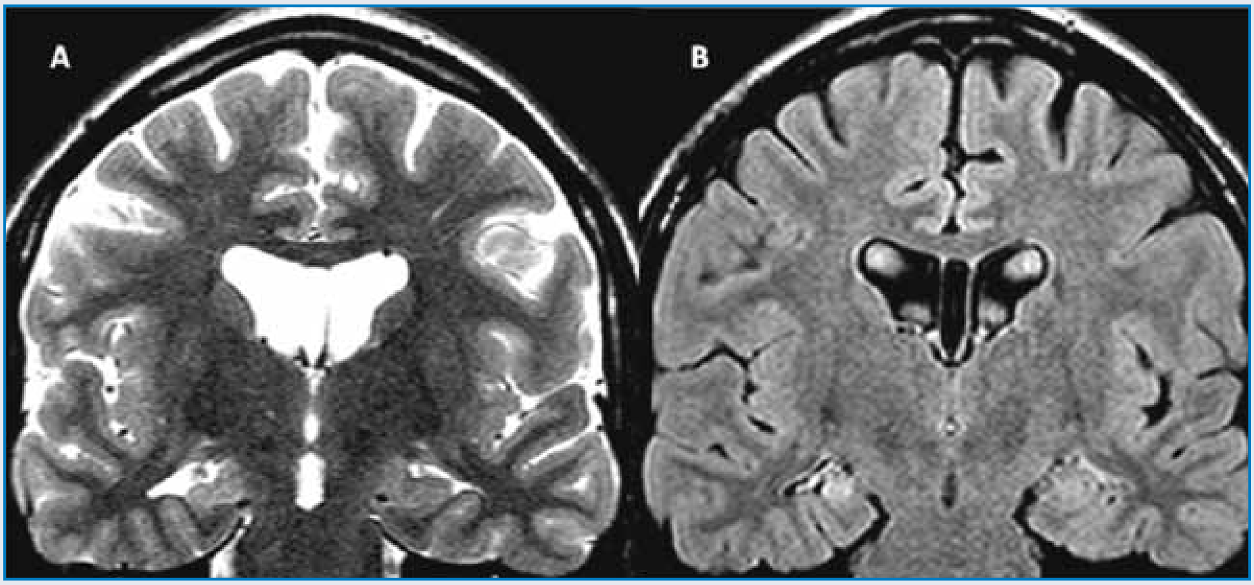

Figure 3: Mapping spatial memory in a patient with hippocampus sclerosis and epilepsy. Figure 3a: A – coronal T2-weighted and B – coronal FLAIR sequences shwowing sclerotic hippocampus on the right. R – right, L – left.

Preoperative mapping of medial temporal lobe memory systems

While the Wada test has been the gold standard for preoperative lateralization of language and memory function, it is invasive and provides only a limited period of time for testing. Other problems associated

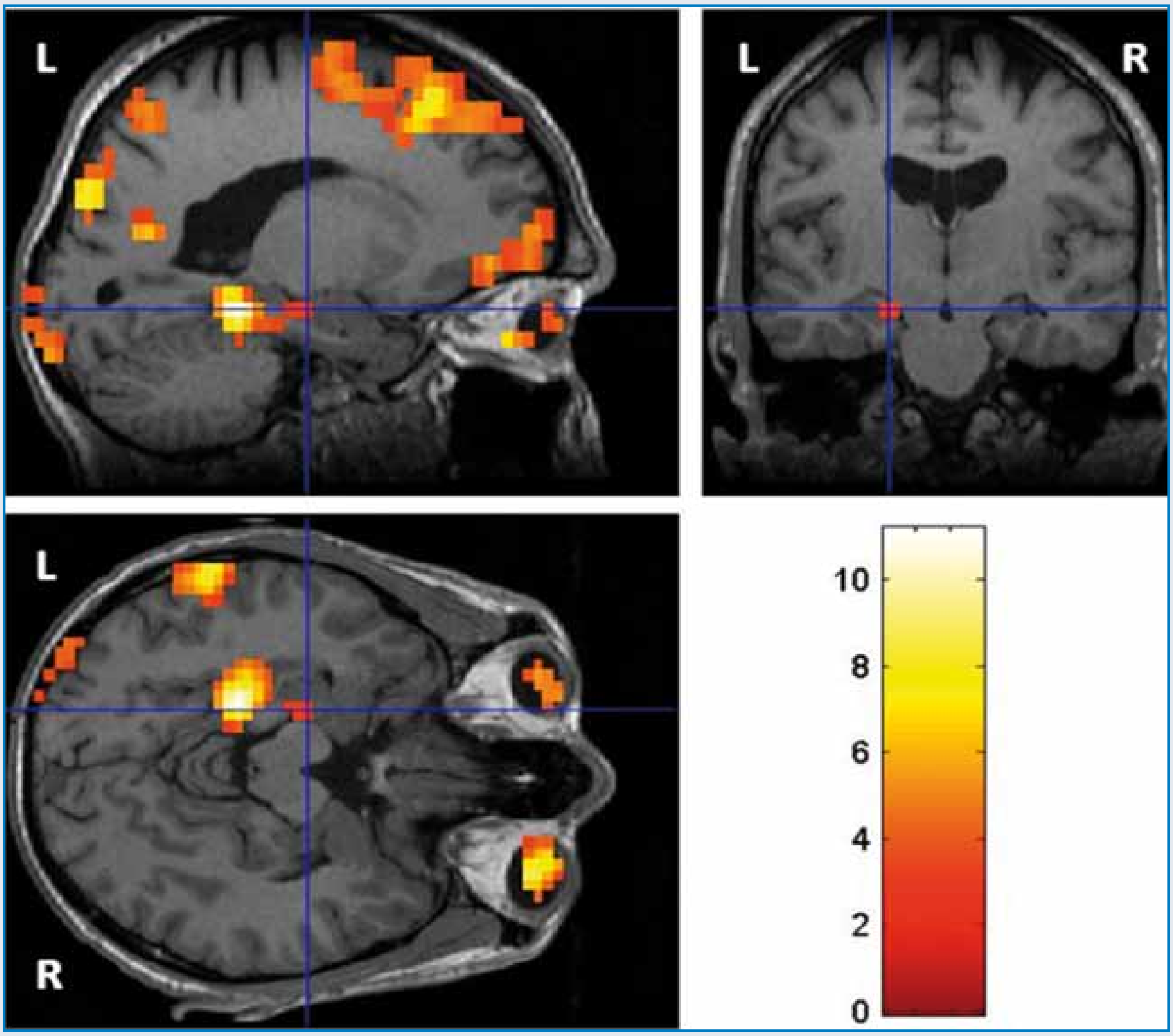

Figure 3b: Roland's hometown walking task. BOLD signal in left hippocampal-parahippocampal area. Healthy controls have fMRI signal in both hippocampal-parahippocampal regions.

with Wada testing include known injection-side order effects [31], variable cross-flow of amobarbital to the contralateral hemisphere, and the fact that the hippocampus is not actually supplied by the anterior circulation and is therefore deafferented rather than directly anesthetized during Wada testing. For these reasons, presurgical mapping of memory function in TLE is an obvious application for clinical fMRI. However, the hippocampus has been notoriously difficult to activate reliably. This may be at least partly attributable to difficulties in disengaging memory function for a control condition, as well as identifying a good active task. The hippocampus is also in a region of comparatively high static susceptibility, resulting in decreased sensitivity for BOLD fMRI. Episodic memory is typically engaged during fMRI by explicit or incidental encoding tasks, with subsequent recognition testing to verify encoding success [32].

Semantic language paradigm have shown activation in medial temporal lobe as well as a network of inferior prefrontal, lateral temporal, cingulate and cerebellar areas [33, 34]. In the majority of patients with mesial TLE hippocampal activation was also demonstrated. There was a significant difference in hippocampal activation between patients with left and right mesial TLE. Right TLE patients showed increased activity in the left hippocampal formation compared with left TLE patients. In contrast, patients with left TLE did not show increased activity in the right hippocampal formation compared with right TLE patients [35] (**Figure 3**).Some studies also compared fMRI memory lateralization with that obtained by Wada testing, demonstrating that memory lateralization by these two modalities agreed to a large extent[36, 32]. However, because fMRI examines endogenous function while the Wada test is fundamentally a lesion study, it is also reasonable to expect that these modalities may differ, and that the findings obtained with each modality may be complementary rather than entirely duplicative [37]. Reductions in fMRI memory activation also appear to correctly lateralize seizure foci in the majority of cases, and some results also suggest that postsurgical amnesia correlates with fMRI activation ipsilateral to the resection [14, 38].

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