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Epilepsy cases: fMRI and MR tractography as qualitative and quantitative tools for proper localization and pre-operative planning.

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Abstract

Introduction: Functional MRI is a relatively new noninvasive brain imaging technique that has been used for neuroscience research applications since the early 1990s. This technique relies on the blood oxygenation level dependent (BOLD) effect. Diffusion tensor magnetic resonance imaging (DTI) is a noninvasive technique that can be used to assess the integrity of cerebral tissue.

Methods: We evaluated 16 patients with unilateral MTLE. We did MRI for language and memory areas for localization and lateralization of the dominating cortical areas concerned with language and memory. Diffusion-weighted images along twelve different directions with a b value of 1000 s/mm2. A 1.5-T scanner was used to acquire those examinations. For DTI we compared the mean diffusivity (MD) and fractional anisotropy (FA) from symmetrical voxels by sampling the basal ganglia, thalamus, hippocampus and parahippocampus regions bilaterally. We compared measurements with the EEG, high-resolution MR imaging, as well as clinical data. For MR tractography, various tracts were traced including the Meyer's loop.

Results: Among the study group only 5 patients with partial epilepsy out of 16 are promising candidates for surgery representing only 31.25 % among the study population 68.75% of our study population were excluded according to our quantitative and qualitative tools.

Conclusion: Combined fMRI with MR tractography are valuable qualitative and quantitative tools for proper localization and lateralization of the eloquent areas including memory, language areas and Meyer's loop in the selection of promising epilepsy surgery candidates and for pre-operative planning.

Introduction:

Brain surgery is an effective treatment for individuals who suffer from medically intractable epilepsy. One common surgical procedure for epilepsy is anterior temporal lobectomy (ATL), which produces long-term cure rates of approximately 60–80%. Common complications of ATL include upper quadrant visual field defects, impairments on naming and other language tasks, and declarative memory deficits. (**Binder et al; 2008**). Thus it has become part of presurgical work-up in potential patients to weigh the risk of memory decline against the chance of seizure relief. The key to estimating the risk of memory decline after surgery is the preoperative assessment of the functional integrity of the tissue to be resected. (**. Frings et al; 2008**). Functional MRI is a relatively new noninvasive brain imaging technique that has been used for neuroscience research applications since the early 1990s. This technique relies on the blood oxygenation level dependent (BOLD) effect, which was first described by Dr. Ogawa and colleagues in 1990. (**Pillai et al; 2007**).

Diffusion tensor imaging (DTI) of the human brain is a relatively new MRI method that allows noninvasive modeling of the diffusive transport of water molecules by means of a diffusion tensor. Of the several indices used to characterize the diffusion tensor, those most commonly used include trace of the tensor, which measures apparent diffusion coefficient and fractional anisotropy. (**. Kimiwada et al; 2006**)

Methods

All patients or their care givers gave informed consent for participation in research.

We evaluated 16 patients with unilateral TLE while excluding the other etiologies of epilepsy. 6 (37.5%) were males and 10 (62.5%) were females. Their ages ranged from 12 to 36 years old with the mean age is 24 years; for males is 19 years and for females is 27 years. Combined fMRI with MR tractography were performed by using Achieva R3.2 (Achieva; Philips Medical Systems, Best, the Netherlands) 1.5T whole-body MR scanner. The following sequences were acquired: T2 weighted sequences, fluid attenuated inversion recovery (FLAIR), T1-weighted sequences.

High-resolution axial T1WI with an inversion-recovery TSE (turbo-spin echo): It was used for anatomical correlation in axial orientation. Its scan time = 2.45min. The used parameters were: TR = 2053ms, TE = 15ms, TI = 350ms, matrix = 256×190, FOV = 220×220, NSA = 1, number of slices = 23, slice thickness = 5mm, with no inter-slice gaping.

3D T1-WI fast field echo (FFE) sequence: It was used in further post-processing steps for multi-planar reformation (MPR). Its scan time = 5:42min. The used parameters were: TR = 22ms, TE = 9.2ms, FA = 300, matrix = 256×256, FOV = 230×230, sense factor = 1.5, number of slices = 200 and slice thickness =1mm with no inter-slice gaping.

A BOLD sensitive single shot EPI technique using T2* sequence was used. Its scan time varies according to the design of the used paradigm. The used parameters were: TR = 3000ms, TE = 50ms, FA = 900, matrix 64×64, FOV 230×230, EPI factor = 39, SENSE factor = 1.8, NSA = 1, number of slices = 23, slice thickness = 5 mm, with no inter-slice gaping.

DT imaging data were acquired by using a single-shot echo-planar imaging sequence with the sensitivity-encoding, or SENSE, parallel-imaging scheme (reduction factor, 2) .The imaging matrix was 112 x 115, with a field of view of 220 x 220 mm. Transverse sections of 2mm thickness were acquired parallel to the anterior commissure–posterior commissure line. A total of 50 sections covered the entire hemisphere and brainstem without gaps. Diffusion weighting was encoded along 12 independent orientations, and the b value was 1000 mm2/sec. Other imaging parameters were as follows: echo time = 108 msec, repetition time = 13,723msec, number of acquisitions = two. The total imaging acquisition time for DTI was 15 minutes and 19 seconds.

It was done offline on a separate advanced Philips workstation (extended work space "EWS") (Release 2.5.3.0; Dell, Round Rock, Tex); Pride software (Philips Medical Systems) which allows: a-For fMRI: Generation of functional maps (SPM), adjustment of cluster size & threshold level, multi-planar reformatting (MPR) and overlay and co-registration of the functional maps on either the axial T1WI with IR or the reformatted 3D high resolution brain volumes. Also the EPI data were motion corrected & interpolated. b-For MR Tractography and for calculation of the DTI indices which is based on the Fiber Assignment by Continuous Tracking (FACT) method which is an algorithm depends on the direction of anisotropy (the principal eigenvector of the diffusion tensor) and proceeds from an initially determined point (or set of points) in the direction of the principal eigenvector from pixel to pixel (continually updating the direction as it assesses each new pixel). This process continues until a predetermined lower FA threshold is encountered, often an FA value of 0.3 or greater than 70° for the trajectory angles between the ellipsoids, at which point the fiber path is terminated. This pixel of lower FA would no longer be dominated by white matter, thus indicating the termination of the tract. Anisotropy was calculated by using orientation-independent fractional anisotropy (FA), and diffusion-tensor MR imaging–based color maps were created from the FA values and the three vector elements. The vector maps were assigned to red (x element, left-right), green (y, anterior-posterior), and blue (z, superior-inferior) with a proportional intensity scale according to the FA. (**Price et al, 2003 & 2004**).

Fractional Anisotropy (FA) and Mean Diffusivity (MD) were measured by placing ROI (Region of interest) on the preferred place on the anatomical diffusion map. MD reflects the average magnitude of molecular displacement by diffusion while FA reflects the directionality of molecular displacement by diffusion. We first examined the conventional MRI images specially the axial and coronal FLAIR sequences searching for any signal abnormality or atrophy or anatomical distortion of the hippocampal and parahippocampal region (mesial temporal sclerosis). Then we started to place ROIs at the hippocampal region, just medial to temporal horn of lateral ventricle on coronal images, other ROIs placed at the putamen and anterior part of the thalamus on axial images bilaterally. Comparison between right and left sides was important as the affected side usually showed significant decrease in FA and increase in MD values which represents the site of eplieptogenic focus. Statistical analysis was done by using the t-test and p-values acquired.

Results

The EEG findings were 10 patients with left temporal focus and 6 patients with right temporal focus.

Conventional MRI findings were three patients with left MTS, one patient with right MTS and one patient with right MTS and right temporal focal dysplasia where there is small to moderate size focal zone of about 1.5x2 cm at the right temporal region cortical and subcortical mostly right mid temporal gyrus.

DTI confirmed the EEG and conventional MRI data in 4 cases out of 5 cases (**Table 1**) as follows:

Age	Sex	EEG	Conventional MRI	DTI
28	M	Left temporal	Left MT	Increased diffusivity of the left hippocampus
16	F	Right temporal	Right MTS	Decreased right hippocampus & para-hippocampus FA and increased ADC
26	M	Right temporal	Right temporal focal dysplasia at the Rt mid temporal gyrus at cortical and subcortical location Mild prominence of the temporal horn of the right lateral ventricle denoting an element of right hippocampal volume loss.	Mild reduction of FA and increased ADC values of the right hippocampus. Slight indentation of the related white matter tracts related to the lesion.
31	F	Left MTS	Left MTS	Decreased left hippocampus & parahippocampus FA and increased ADC

Table (1): DTI results confirming conventional MRI

DTI added to the conventional MRI data in 4 cases where the conventional MRI data were unremarkable yet the DTI added data to the MRI studies were concomitant with the EEG studies (**Table 2**).

Age	**Sex**	**EEG**	**Conventional MRI**	**DTI**
21	F	Left temporal epileptic discharge	Unremarkable	Decreased left hippocampus FA
21	F	Right temporal	Unremarkable	Mild reduction of FA and increase of ADC values of all the right sided gray matter than the left suggesting element of structural disorganization or cellular loss on the right side Slight reduction of FA and increased ADC values in right cingulum and Arcuate fasiculus.
26	F	Right temporal	Unremarkable	Decreased right hippocampus, basal ganglia and to a lesser extent thalamus FA and increased ADC values.
32	F	Right temporal	Unremarkable	Decreased right hippocampus, basal ganglia and the thalamus FA values.

Table (2): DTI results adding to the conventional MRI

Measuring FA and ADC values of the hippocampal formation (HF) our study group of patients with TLE revealed significant reduction in FA and increase in ADC in the affected side as compared to the normal side. The mean FA value of the diseased side is 0.183 as compared to normal side 0.264. The mean ADC value of the lesion side is 1.143 × 10-3 mm2/s as compared to 0.954 × 10-3 mm2/s of the normal side.

Tractography Findings were two cases showed abnormal finding in which one patient with right temporal focal dysplasia and right MTS that had been verified by slight indentation of the related white matter tracts related to the lesion and the other patient showed the right side white matter tracts were reduced in size in qualitative comparison to the left side. The other 14 cases show normal MR pattern regarding direction, color maps and color hues with no displacements and no interruptions. Also Tractography was used for delineating the Meyer's loop in all patients.

fMRI findings for language were right hemispheric dominance was detected in one male patient, left hemispheric dominance was detected in eight patients and equivocal bilateral representation was detected in seven patients (**Table 3**).

The language centers representation	**Right**	**Left**	**Bilateral**
Broca's	0	6	10
Wernicke's	1	7	8
Overall	1	8	7
Males	1/1	3/8	2/7
Females	-	5/8	5/7

Table (3): The different patterns of hemispheric dominance concluded by different language paradigms in relation to patients' sex.

fMRI findings for memory were lateralization of memory was possible in 15 patients out of the 16 patients. The failed memory task was recorded in female patient because of the head movement and non compliance. Otherwise one female patient showed right hippocampal activation, seven patients showed unilateral left hippocampal activation among them three were males and four were females and also seven patients showed bilateral equivocal hippocampal activation among them three were males and four were females (**Table 4**)

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The episodic memory representation	**Rt dominance=1**	**Lt dominance=7**	**Equi-dominance=7**
Hippocampus	1	7	7
Males	-	3/7	3/7
Females	1/1	4/7	4/7

Table (4): The different patterns of hemispheric dominance concluded by different memory paradigms in relation to patients' sex.

Among the study group only 5 patients with partial epilepsy out of 16 are promising candidates for surgery (**Table 5**) representing only 31.25 % among the study population 68.75% of our study population were excluded according to our quantitative and qualitative tools.

Age	Sex	EEG	Conventional MRI	DTI	fMRI for language	fMRI for memory
16	F	Right temporal	Rt MTS	Decreased right hippocampus & parahippocampus FA and increased ADC	Left Broca's and Wernicke's	Left Hippocampus
26	M	Right temporal	Right temporal focal dysplasia at the Rt mid temporal gyrus at cortical and subcortical location	Mild reduction of FA and increased ADC values of the right hippocampus.	Left Broca's and Wernicke's	Left Hippocampus
31	F	Left MTS	Left MTS	Decreased left hippocampus & parahippocampus FA and increased ADC	Bilateral Broca's and Wernicke's more dominant on the left side	Bilateral Hippocampus more dominant on the left side
32	F	Right temporal	Unremarkable	Decreased right hippocampus, basal ganglia and the thalamus FA values.	Bilateral Broca's and Wernicke's more dominant on the left side	Bilateral Hippocampus
17	M	Left temporal	Left MTS	Unremarkable	Left Broca's and Wernicke's Right Broca's on the word antonym paradigm and Right Wernicke's word generation paradigm	Bilateral Hippocampus

Table (11): results of the promising candidates for surgery.

Only one patient with left MTS underwent selective tailored left amygdalo-hypocampectomy, the neurosurgeons were very conservative with our resection because of the left sided approach (afraid to loose memory or language functions postoperatively), But fortunately the patient's memory and language functions postoperatively are perfect, and his seizures are controlled.

Discussion

The BOLD fMRI has long been accepted as a powerful research technique in cognitive science and neuroscience and has recently gained acceptance as a clinical tool for pre-operative brain mapping (**Zheng et al., 2007**). It assesses brain activity indirectly via detection of local hemodynamic changes in capillaries and draining veins of functional areas. The blood-oxygen-level- dependent (BOLD) technique makes use of blood as an intrinsic contrast agent. BOLD signals have been shown to reflect actual neuronal activity with high spatial accuracy (**Logothetis & Wandell, 2004**).

In a review by **Baxendale (2002)**, 70 patients were found in the literature that had undergone both fMRI language studies and Wada testing. With the exception of one study (**Worthington et al.,1997**), which showed a comparatively low concordance of only 75% with a verbal fluency task used as fMRI paradigm, all other report impressive concordance rates between the two techniques despite the use of different language tasks and Wada test protocols. Selective language deficits have been reported following language-dominant ATLR, with naming the most commonly affected function (**Davies KG et al., 1998**). It has also been suggested that the risk for post-operative decline in naming abilities increases with age of seizure onset and the extent of lateral temporal neocortex resected (**Hermann et al., 1999**).

One study has used pre-operative functional neuro-imaging to predict language deficits following left ATLR. Temporal lobe fMRI asymmetry was found to be predictive of deficits seen on a post-operative naming test with a greater degree of language lateralization toward the left hemisphere related to poorer naming outcome and language lateralization towards the right hemisphere associated with less or no decline. The correlation between temporal lobe fMRI and naming deficits was stronger than that seen in the frontal lobes and also stronger than that between IAT and naming deficits (**Sabsevitz DS et al., 1998**).

Interestingly, many patients do not suffer any language deficits following ATLR, suggesting that multiple sets of neural systems may exist that are capable of performing the same cognitive function, and that some of these may be engaged following focal brain injuries. In a study of patients who had undergone left ATLR but did not have deficits in sentence comprehension, decreased activation was demonstrated in undamaged areas of the normal left hemisphere system but increased activation was seen in several right frontal and temporal regions not usually engaged by normal subjects. This suggests that there is more than one neural system capable of sustaining sentence comprehension. This study was, however, unable to tell whether this functional reorganization to the right inferior frontal gyrus occurred pre or post-operatively (**Noppeney et al., 2005**).

A separate study looked at the role of the right inferior frontal gyrus by comparing its functional activation on a verbal fluency task in controls with left TLE patients. The patients were shown to activate a more posterior right inferior frontal gyrus region compared with controls, although left inferior frontal gyrus activation did not differ significantly between the two groups. Further, verbal fluency-related activation in the right inferior frontal gyrus was not anatomically homologous to left inferior frontal gyrus activation in either patients or controls. This suggests that reorganization takes place pre-operatively in patients with chronic left TLE, and that the prediction of language outcome following left ATLR may depend not only on the extent of preoperative right hemisphere activation, but also its location (**Voets NL et al., 2005**).

It could be shown that fMRI of memory function can be used to predict post surgical memory outcome in patients undergoing temporal epilepsy surgery in a clinical setting. It was shown that increased activation ipsi-lateral to the seizure focus is associated with greater memory decline. The detected asymmetry ratios in the medial TL was correlated significantly with memory lateralization by IAP testing (**Rabin et al.,2004; Janszky et al.,2006; and Richardson et al.,2004**).

Bonelli et al., (2010) have shown that memory fMRI is the strongest predictor for postoperative verbal and visual memory decline in individual subjects using a material specific memory encoding paradigm compared to other previously suggested predictors. **Bonelli et al., (2010)** results support the functional adequacy theory, suggesting that it is the capacity of the ipsi-lateral hippocampus, most likely the remaining posterior part, which preserves verbal and visual memory encoding function after ATLR.

Cheung et al., (2009) study shows the postoperative memory performance was significantly associated with functional activation contralateral to the side of resection in patients with unilateral TLE, and the function of the contralateral mesial temporal lobe might play an important role in supporting memory performance after temporal lobe resection.

The combination of fMRI to identify cortical regions involved in language function and MR-tractography to visualize white matter pathways connecting these regions offers an opportunity to study the relationship between structure and function in the language system. The combination of fMRI with information on the structural connections of these normally and abnormally functioning areas offers the opportunity to improve understanding of the relationship between brain structure and function and may improve the planning of surgical resections to maximize the chance of seizure remission and to minimize the risks of cognitive impairment (**Thornton R. et al, 2009**).

Precise preoperative assessment of the epileptogenic focus is a prerequisite for good surgical outcome in patients with MTLE. Spike origin and propagation might result in metabolic and physiological changes in brain tissues, which further affect water diffusion. Thus abnormalities induced by epilepsy can be detected by DTI. (***Ai-hong et al, 2006***)

DTI is a significant advancement in the field of diagnostic imaging. It is, in fact, the only method capable of displaying cerebral white matter tracts in vivo, and it has been shown that this knowledge can assist the neurosurgeon in preoperative planning (***Yu et al., 2005***).

Taoka et al., (2008) evaluated 14 patients who underwent temporal lobe resection surgery for temporal lobe epilepsy. In these patients, diffusion tensor tractography was used to delineate the Meyer loop and then the interindividual variation of its anterior limit was evaluated. Diffusion tensor tractography indicated that interindividual variation in the position of the Meyer loop can be quite large, which suggests that the extent of the temporal lobe resection seen with conventional imaging might not predict the post surgical visual field defect. When using diffusion tensor tractography to evaluate the Meyer loop before surgery, post surgical visual field defects more precisely could be predicted.

Temporal resection, including anterior temporal lobectomy or selective amygdalo-hippocampectomy, is a widely accepted surgery for temporal lobe epilepsy. However, this method sometimes can cause optic tract injury in the temporal lobe (the Meyer loop), which may lead to a “pie in the sky” shaped visual field defect after the surgery. The degree of the visual field defect that has been reported depends upon the anatomic range of the resection (***Taoka et al., 2008***).

Conclusion

Combined fMRI with MR tractography are valuable qualitative and quantitative tools for proper localization and lateralization of the eloquent areas including memory, language areas and Meyer’s loop in the selection of promising epilepsy surgery candidates and for pre-operative planning.

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حالات الصرع: دور كلا من fMRI و MR tractography كأدوات كمية و كيفية للتحديد الموضعي السليم و التخطيط لما قبل العملية

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مقدمة:

التصوير بالرّنين المغناطيسي الوظيفي للدماغ هي تقنية جديدة غيرِ منتشرةِ نسبياً حيث إستعملتْ لتطبيقاتِ بحثِ عِلْمِ الأعصاب منذ أوائلِ التسعينياتِ. هذه التقنيةِ تَعتمدُ على تدفق الأكسجين في الدمِّ بمستوى عالي . الإنتشار تصوير رنينِ tensor المغناطيسي (دي تي آي) هي تقنية غير منتشرة التي يمكن أن تُستَعملَ لتَقييم سلامةِ النسيجِ المخّيِ.

الطرق:

قمنا بتقييم 16 مريضا مع MTLE من جانب واحد . فعلنا الرنين المغناطيسي الوظيفي للغة والمناطق الذاكرة لتوطني و lateralization من المناطق القشرية التي تسيطر المعنية اللغة والذاكرة .نشر الصور على طول المرجحة 12 اتجاهات مختلفة ذات قيمة AB من s/mm2. 1000 تم استخدام الماسح الضوئي T 1.5 للحصول على تلك الاختبارات ل DTI قارنا متوسط انتشارية (MD) وتباين كسور (FA) من voxels متناظرة من أخذ عينات من العقد القاعدية، المهاد، وقرن آمون مناطق مجاورة الحصين ثنائيا . قارنا القياسات معEEG ، التصوير عالية الدقةMR ، وكذلك البيانات السريرية .لـtractography MR، وتتبع مساحات مختلفة بما في ذلك حلقةماير .

النتيجة:

استبعدت من بين مجموعة الدراسة فقط 5 من المرضى الذين يعانون من الصرع الجزئي من أصل 16 مرشحين واعدة لجراحة تمثل سوى 31.25٪ بين السكان الدراسة 68.75٪ من السكان وفقا لدراستنا أدواتنا الكمية والنوعية.

الخلاصة: الرنين المغناطيسي الوظيفي المشتركة مع tractography MR هي قيمة ونوعية الأدوات الكمية لتوطين السليم و lateralizationمن المجالات بما في ذلك مجالات بليغة الذاكرة واللغة، وحلقة ماير في اختيار المرشحين واعدة لجراحة الصرع والتخطيط قبل العملية .