Investigation of human brain function by applying neuroimaging techniques available in clinics

Ph.D. thesis

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Preface

I have started my studies in the field of magnetic resonance imaging (MRI) in 2005 as a PhD-student of Pécs University Medical Faculty. I have tried to learn as many methods as I could (diffusion-weighted imaging (DWI), diffusion-tensor imaging (DTI), volumerty, relaxometry, MR spectroscopy), however, most of my results have come from functional MRI (fMRI) studies on the clinical scanner of the Pécs Diagnostic Institute (PDI) operating at low-field (1T). Under the supervision of my mentors and Dr. József Janszky, we were the first in Hugary who applied fMRI routinely as a part of neurosurgical evaluation. I have taken part in optimizing image acquisition and data analysis as well as determining and broadening its clinical application. Collaboration with an NMR laboratory of the Max Planck Institute in Göttingen was a great help, resulting in two methodological articles. Owing to the cooperation with the Department of Neurology and the PDI I have got the opportunity to investigate pathological and normal cognitive processes, resulting in 4 Hungarian and 9 international publications altogether.

Efficiency the fMRI on human MR scanner operating at 1T available in our clinics was demonstrated by half thousand successful examination; however, the hundreds of measurement helping the recovery of half hundred patients have at least so much importance.

Acknowledgments

The work involved in this thesis could not have been carried out without enormous help from a number of persons, to whom I owe a great debt of gratitude and whom I would like to thank for their valuable contribution.

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I would also like emphasize my deep gratitude towards József Janszky and Prof. Sámuel Komoly, for welcoming me to the Department of Neurology; and for providing their knowledge and insight in the field of neurology.

Many thanks are also due to Prof. Ferenc Gallyas, as being my first supporter in the field of neuroscience. The invaluable discussions with him regarding the mysteries of the living tissue in the central nervous system have given me unique thinking. Furthermore, I would like to thank Béla Németh, Ferenc Kövér and Péter Bódi at the Pécs Diagnostic Center for granting me a workplace and all the technical and financial support.

I also owe my gratitude to Prof. Jens Frahm and his colleague, Klaus-Dietmar Merboldt, at the Max Planck Institute for Biophysical Chemistry, Göttingen, Germany, for extending my know-how in MRI methods.

Last but not least, I express my gratitude to my family for their love and support.

Abbreviations

BOLD	Blood Oxygenation Level Dependent
BW	(receiver) BandWidth
DTI	Diffusion Tensor Imaging
DV	Déjà Vu
EEG	Electro-EncephaloGram
EPI	Echo Planar Imaging
fMRI	functional Magnetic Resonance Imaging
FT	Fiber Tracking
IWG	Internal Word Generation
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NMR	Nuclear Magnetic Resonance
PET	Positron Emission Tomography
PFM	Passive Finger Movement
ROI	Region Of Interest
SFO	Sequential Finger Opposition
SISCOM	Subtraction Ictal SPECT Co-registered to MRI
SNR	Signal-to-Noise Ratio
SPECT	Single-Photon-Emission Computed Tomography
SPM	Statistical Parametric Mapping
T	Tesla (measure of magnetic field strength)
T_2*	effective Transversal/Spin-Spin Relaxation Time
TE	Echo Time (time between the excitation and the acquisition)
TR	Repetition Time (time between two excitations)
TTC	Two-Threshold Correlation

Introduction

Previously, magnetic resonance imaging (MRI) in humans has been applied merely to examine anatomical and pathological macrostructure of the brain. Novel techniques, however, enable us to obtain an insight into the microstructure and to investigate and even to visualize the function of the human brain. The potential and applicability of these techniques have not been widely studied in Hungary because of three main reasons: (a) with very few recent exception (Philips Achieva 3T system in Budapest and Siemens TIM Trio 3T system in Pécs), there are no experimental MR systems in Hungary; (b) additionally the clinical MR scanners – they are usually operating at lower-field (0.5-1.5T) – are generally loaded with routine measurements and machine time has not been devoted to state-of-the-art experiments; (c) most researchers are convinced about that a higher field strength is unquestionably superior when applying novel techniques. This situation has resulted in a large gap in MR knowledge between Hungary and more developed countries. During my Ph.D. training, I have pushed hard to convince other scientists about applying these **techniques** – **with optimized settings** – also **at lower-field** to make them **accessible** widely. It is at least so important, that they can also be of service to the patients, who can be managed better clinically, for instance at the stage of preoperative neurosurgical planning, intraoperative functional neuronavigation or monitoring and – with the help of e.g. neurofeedback – intensifying their postoperative rehabilitation.

Investigating brain functions by means of MRI

The main goal of neurosurgical evaluation is to reduce the damage of brain functions during intervention to its minimum. To preserve the so called eloquent brain areas, we have to determine their individual locations precisely. There are numerous invasive procedures to achieve this: with help of intracarotid amobarbytal (Wada-test) we can determine in which

hemisphere the area responsible for a given function is located. Stimulation applying subdural electrodes and intraoperative sensory evoked response examination give more accurate results. Disadvantage of these examinations are their requirement of special devices and their high invasiveness – sometimes they need for surgery.

Recently more widespread FMRI is feasible to visualize brain functions with high spatial and temporal resolution and lack of invasiveness. There is a growing literature about its responsibility proved to be similar to that of invasive procedures. It enables us to determine whether a tumor or epileptogenic center takes part in a brain functions accessible with fMRI. With its help we can increase surgical safety without necessity of preoperative and invasive investigations encumbering both the patient and staff as well as increasing expense.

Since Roy and Sherrington (1896), it has been known that changes in blood flow and blood oxygenation in the brain are closely linked to neural activity (neurovascular coupling). This finding also provides the base of positron emission tomography (PET). Almost one hundred years after Roy and Sherrington, Fox and coworkers have found that the increase in cerebral blood flow is higher than that of O_2-consuption, resulting in a local decrease in the relative deoxyhemoglobin level. Based on this finding, Ogawa and coworkers developed a technique to record local brain activity depending on the local level of O_2 (or rather local relative level of deoxyhemoglobin). This technique is called blood oxygenation level dependent (BOLD) imaging. Roughly, in an activated brain region the local decrease in the relative level of the paramagnetic deoxyhemoglobin causes decreased magnetic susceptibility leading to slower T_2*-relaxation, causing elevated signal in T_2*-weighted images, which can be detected using an MRI scanner.

Statistical evaluation

The aim of evaluating fMRI dataset is to classify the voxels as active, deactive or none. In the

end, similarly to any other statistics, we have to declare level of significance or threshold. And also as a statistical method, it may produce false positive and negative results. Because of the great number of estimation (at a common spatial resolution of $3x3x3mm^3$, we have about 50000 voxels), risk of false positives is much higher; therefore a simple threshold would surely give false result.

Apart from different correction methods coming from statistics, such as controlling False Discovery Rate (FDR) or FamilyWise Error (FWE) rate, there are approaches taking account physiological properties of neurovascular coupling.

The most widespread method is, besides setting a threshold on a statistical basis, applying a second threshold on the basis of number of concurrently activated neighboring voxels (aka cluster extent). It can also be used in Statistical Parametric Mapping (SPM), which is the most commonly used software for analyzing functional datasets. A potential drawback of this method is that it requires subjective thresholding. Generally, as the statistical threshold decreases, the volume of "true" activation increases (as more and more voxels survive it), but at some point we will see a lot of "scattershot" (false positive) clusters throughout the brain. At that point we should back off to use a more stringent criterion. When preparing results e.g. for a neurosurgical intervention, we can try to maximize the area of activation with minimal false positives in the vicinity of the area of intervention. Visualizing the activation across multiple planes sometimes clarifies whether scattered activation along the fringes of a tumor is part of a larger cluster. Moreover at lower threshold we can “eliminate” the small clusters simply with increasing the extent threshold. Sometimes, however, at lower statistical threshold these small (false positive) clusters build up for a bigger one hard to eliminate.

On the other hand a fMRI data processing method has been established that emerges as a rather simple data-driven approach originally motivated by detailed experimental observations and physiologic considerations. The method is referred to as Two-Threshold

Correlation (TTC) and has evolved during the analysis of several thousands of fMRI data sets acquired in multiple studies of the Göttingen laboratory. It is based on cross-correlation, which – like linear regression – examine similarity of signal intensity changes to HRF, and characterize it with correlation coefficient (CC). The CC maps are thresholded individually by estimating the noise distribution underlying the distribution (or histogram) of correlation coefficients of the *actual* fMRI acquisition. In fact, studies without any stimulation (Null experiment) demonstrated that the width of a corresponding CC distribution may be affected by alterations of the hemodynamic responsiveness (`arousal'), respiration, perfusion, flow-induced tissue pulsations, or motions. Because the basic form of these distributions is adequately described by a Gaussian curve, true brain activations, that is voxels representing paradigm-associated fMRI signal alterations, may be easily identified: the CC histogram of a fMRI study emerges as the sum of a dominating noise distribution and a second much smaller distribution of activated voxels with high positive (or negative) CC values. In contrast to methods based on a single threshold, the TTC method employs two probabilistic thresholds for their separation: a high value for the identification of highly significant activations and a lower value for limiting the iterative addition of directly neighboring voxels to these centers. The approach ensures both specificity and sensitivity for defining the spatial extent of significant activation spots. So, if – similarly to the example above – we want to maximize the area of activation in the vicinity of the area of intervention, just decreasing the lower threshold will not result in "scattershot" (false positive) clusters throughout the brain.

Group analysis

Functional magnetic resonance imaging of human brain activation is a non-invasive method for monitoring hemodynamic responses to a functional challenge in single subjects with high spatial and temporal resolution. However, in view of increasingly complex cognitive

paradigms that often involve only subtle differences in neural activity, the response strengths tend to decrease and impose severe challenges for adequate post processing. In addition, in longitudinal or cross-sectional studies, we are usually looking for activation characterizing a group of subjects. A common strategy is therefore to move from single subject to group analysis, which is also incorporated into SPM. Though elegantly designed for the statistically trained and experienced researcher, a potential drawback of the method is its complexity even at single subject level. As a consequence, SPM applications require substantial knowledge with the potential risk that the rank-and-file user may be misguided to produce inadequate results.

On the other hand TTC has already been published, that circumvents the not only the problem of false positive activation but also the inconvenience of subjective thresholding (see above). Nevertheless, the great advantages of TTC could have utilized only at single subject level.

FMRI in neurosurgical evaluation

During neurosurgical interventions, apart from saving the patient's life, we also try to preserve brain regions which contribute significantly to normal brain process. This is true even more in epilepsy surgery as not a life-saving operation. The "insignificant" contribution of a region can be resulted due to representation of certain brain processes in a network; and one region removed from this network will be compensate by the other network elements (for example in the case of functions with bilateral representations the region contralateral to the resection can also represent the functions of the removed structure). Brain regions thought to be contributed significantly in the healthy brain functions without compensatory reorganization capacity are called "eloquent" areas. One of the challenges in neurosurgical evaluation is to differentiate eloquent areas from the other brain tissue and to determine their relationship to the area of intervention. Numerous studies demonstrated reliability and

reproducibility of fMRI examinations, which resulted in a wide distribution of fMRI methods in neurosurgical evaluation.

One of the most frequent neurosurgical interventions is the operation of temporal lobe epilepsy (TLE), which is superior to drug therapy in curing TLE and lead to complete cessation of seizures in 60-90%. The possible side-effect of the operation, which usually involves mesiotemporal resection, may be memory impairment, because the mesiotemporal structures play a crucial role in memory functions. The intracarotid amobarbytal (Wada) test is the "gold standard" for testing the memory functions of the mesiotemporal structures and for predicting the postoperative memory problems. A numerous publications have showed that, by using fMRI, more patients can be investigated more easily than in Wada test and the results can be compared with normal subjects due to its non-invasive nature.

In almost all cases of neurosurgical interventions, to avoid postsurgical speech distubances, language lateralization has to be known prior to epilepsy surgery. FMRI can be used in the majority of patients otherwise undergoing the Wada test, because speech-activated fMRI acquisition and assessment have become easy and reproducible.

Besides areas concerning memory and language, other eloquent brain areas such as visual system and senso-motor system can also be routinely visualized by fMRI, which makes the neurosurgical evaluation and determining the extent of resection more easily.

Studying pathomechanism of human epilepsy by fMRI

At present, fMRI combined with simultaneous EEG (EEG-fMRI) can demonstrate epileptic functional disturbance with the highest spatial and temporal resolution providing a unique opportunity to study the pathophysiology of epilepsy in humans. Although the technique is not available or not used in most neurosurgical centers, in the future it can be one of the major tool in identifying pathological electrophysiological event in epilepsy and their site of origin

("spike mapping"). Moreover, it is a novel method in investigating sleep and its disorders, too.

However, it has its own limitations. Scalp EEG detects electric potential fields some distance from the source, resulting in very low spatial resolution. The invasive intracranial EEG can only measure electrical changes during epileptic seizures that are in the vicinity of the electrodes. Because the whole brain cannot be implanted by electrodes, a sampling error must always occur during intracranial recordings, thus neuronal activity distant from the electrodes remains undetected. Using ictal SPECT or PET, epileptic activity can only be visualized at the time of the tracer binding, thus it often visualizes seizure spread but not seizure onset.

It is well known that regional increases in brain perfusion coincide with ictal activation. In addition, epileptic seizures are accompanied by abnormally large neuronal activity able to produce hemodynamical changes detected with FMRI much better in comparison with normal neuronal processes. Consequently, spatiotemporal visualization of epileptic activity can be the first step in developing methods to demonstrate whole-brain neuronal activity in general, with adequate resolution in time and space. Hence, there is a growing literature concerning the detection of blood oxygen-dependent (BOLD) signal changes during epileptic seizures, including clinical and subclinical ictus, however, there is no study that successfully demonstrated whole-brain, spatiotemporal, haemodynamic changes during a clinical seizure.

Diffusion Tensor Imaging

FMRI allows for a noninvasive visualization of functioning brain areas, but has limited info about connections and white mater. The absence of activation – e.g. after traumatic brain injury (TBI) – can be caused by either the damage of the brain area or the damage of the connection to that area. If we want to determine the severity and the likelihood of possible outcomes, the information about connections is also necessary.

Diffusion tensor imaging (DTI) can measure anatomical connectivity between areas with MR. Although it is not strictly a functional imaging technique because it does not measure dynamic changes in brain, the measures of inter-area connectivity it provides are complementary to images of function provided by BOLD fMRI.

The basic principles of 'plain' diffusion MRI were laid out in the mid 1980s. With its help tissue structure can be examined at a microscopic level well beyond the usual MRI resolution. During typical diffusion times of about 50-100 ms, water molecules move in the brain on average over distances around 10-15 μm, bouncing into, crossing or interacting with many tissue components, such as cell membranes, fibers or macromolecules. In more pathology, changes in the diffusion can be observed in a very early phase; proved to be extremely useful in routine diagnostics. The most successful application of diffusion MRI since the early 1990s has been acute brain ischemia.

Furthermore, as diffusion is truly a three-dimensional process, molecular mobility in tissues is not necessarily the same in all directions, as it was already detected for the first time in vivo at the end of the 1980s in white matter. This diffusion anisotropy may result from the presence of obstacles, especially the ones with directionality (e.g. bundles of more or less myelinated axonal fibers), that limit molecular movement differently in each directions. It was quickly apparent that this feature could be exploited to map out the orientation in space of the white matter tracks in the brain, assuming that the direction of the fastest diffusion would indicate the overall orientation of the fibers. Work on diffusion anisotropy really took off with the introduction in the field of diffusion MRI of the more rigorous formalism of the diffusion tensor (DT), by Basser and coworkers. With the formalism of tensor, a property – in this case, diffusion anisotropy effects – can be extracted, characterized and exploited along more axis of a coordinate system – in this case, the space – providing even more exquisite details of tissue microstructure. Many studies have been published thereafter dealing with the optimization of

the MRI sequences necessary to get access to the diffusion tensor, the processing and the display of DTI data, and of course, potential applications. After evaluating DT-data, fractional anisotropy (FA) describing the diffusion profile of the water can be obtained. FA can have a value between 0 (perfectly isotropic – spherical profile – diffusion) and 1 (infinitely anisotropic – infinitely elongated profile – diffusion).

The most advanced application is certainly that of fiber tracking (FT) in the brain, which can visualize the neural tracts with tracking the DT. This technique is able to detect damage of the tracts and other alterations, such as TBI, brain tumor or multiple sclerosis; or even pathological connectivity in dyslexia or schizophrenia. In combination with fMRI, it might open a window on the important issue of functional networks.

Low magnetic field

Because the MRI-detectable hemodynamic response to a change in neural activity depends on the microscopic magnetic susceptibility changes that are induced by changes in the absolute concentration of deoxyhemoglobin, its sensitivity is commonly expected to increase with the strength of the static magnetic field. So far, only a limited number of low-field functional MRI studies have been reported in the literature. In fact, all comparative studies using echo-planar imaging (EPI) at a high and low field indicated that a higher field strength is unquestionably superior, so that the authors of a successful functional MRI study at 1 T felt tempted to disqualify their own results as "somewhat controversial". However, the increased sensitivity to macroscopic susceptibility artifacts at higher fields is certainly disadvantageous for many clinical conditions (e.g. examining mesiotemporal structures or in the vicinity of air-filled cavities and sinuses). Furthermore, neurosurgical patients who underwent a preceding brain operation may have defects in skull bone which also result in severe susceptibility artifacts compromising EPI of residual neighboring tissue – the obvious target of functional

MRI studies in these cases.

In our country, most of the MR-scanners are operating at lower field (maximum 1.5Tesla), known to have lesser sensitivity and worse signal-to-noise ratio (SNR). Moreover, producers of scanners are also urging to buy newer, more modern machines capable of novel techniques. However, thanks to the technical developments, with modern scanners operating at low field better homogeneity and formidable sensitivity in detection can be achieved. Therefore, methods having required higher field earlier (such as fMRI) can now be conducted at low field, too; even with intraoperative scanners usually operating at lower than 1.5T.

With proper settings of acquisition parameters and appropriate post-processing methods sensitive enough to detect activation at low field, possibility of applying novel imaging techniques becomes in reach of wider community: It would extend the diagnostic possibilities for a wide spectrum of neurological/neurosurgical patients, would enable us to utilize low-field (and usually cheaper) scanners for screening; and would provide its useful methods for neuroscientists. For all, who have access only to low-field MRI systems.

Limitation of FMRI

FMRI can detect brain activity without any radioactive agent in comparison with SPECT or PET. To our present knowledge it is completely noninvasive, making fMRI usable several times in case of monitoring, screening or conducting a complex cognitive study. Its superiority in spatial resolution and availability (in terms of both presence and price) are also unquestionable.

In other hand, due to its low sensitivity, more repetitions of a task are needed, which limits its usability. Single or rare events with longer duration – such as seizures and other 'ictal' events – are hard or impossible to detect with fMRI. The other main limitation is that not everyone can be put into scanner: e.g. epilepsy patient with large movement, small children, subject

with pacemaker or tattoo; or even with enlarged abdominal circumference caused by overweight. This latter is a growing problem in e.g. United States.

Although, there is no one-for-all procedure, and sometimes we have no choice but to use the only one suitable; there is a trend to move towards fMRI, because – regarding to all aspects – fMRI is the best candidate for routine diagnostic purpose and neuroscientific research as well.

Aims

- (i) to optimize both image acquisition parameters and post-processing appropriate for reliable low-field functional MRI studies and (ii) to assess its reliability in comparison to acquisitions at 3T

- to demonstrate its feasibility in routine diagnostics: both in preoperative neurosurgical evaluation and intraoperative functional neuronavigation, as well as postoperative control

- (i) to develop a new approach in group analysis of fMRI data with all the advantages of TTC and (ii) to prove its reliability comparing its results to corresponding group analyses with SPM

- by means of ictal-FMRI during an epeileptic seizure at low magnetic field, (i) to highlight the site of the initial haemodynamic alteration (i.e. putative seizure-onset zone) and (ii) to visualize haemodynamic changes associated with seizure propagation

- to determine the level of the functional and structural damage in the algorithm of work-up of a patient suffering from severe traumatic brain injury (TBI) with combining fMRI with DTI both performed at low magnetic field, and comparing the DTI-results with that of a healthy subject

- to visualize brain activity during Déjà Vu (DV) by applying suitable functional neuroimaging (SPECT)

Results

1. Recording neural activities by means of MRI at low magnetic field

1.1. Optimizing parameters at low magnetic field

To maximize the signal-to-noise ratio (SNR) lower spatial resolution (3.1 x 3.1 x 5 mm), longer repetition time (TR = 2000 ms) and the longest spectral bandwidth (BW = 752 Hz) available were applied. Among the parameters to be optimized, longer echo time (TE = 80 ms) should be emphasized, which provides an adequate compensation the lower sensitivity of the lower filed strength to magnetic susceptibility. Longer TE decreases SNR drastically, however, increases T_{2*} contrast

Later – to increase spatial resolution – longer TR (TR = 2500 ms) was used, so we was able to reach 3 x 3 x 3 mm (isotropic) resolution. With these settings, we could acquire fMR images with good quality during applying clinically relevant paradigms, such as internal word generation (IWG), sequential finger-to-thumb opposition (SFO), passive finger movement (PFM) and mental navigation.

1.2. Comparing fMRI at field strength of 1T and 3T

Our results acquired at low field were compared those provide by measurement at high field (3T). The same temporal (TR = 2500 ms) and spatial (3 x 3 x 3 mm) resolutions were applied at both field strengths. On the other hand, other parameters were set to be optimal at the given field strengths. The same eight subjects were examined using IWG, SFO and PFM paradigms. Analysis was accomplished with "gold-standard" SPM5, as well as with TTC.

Single-subject analysis done with SPM5 showed three times more activated pixels at 3T than at 1T in the Broca's and sensomotor areas. TTC, however, resulted in same amount of activated pixels at both field strengths; which amount was the same as that resulted from

SPM5 analysis of data acquired at 3T. Group-analysis done with SPM5 resulted in almost equal amount of activated pixels at both field strengths.

In conclusion, adequate post-processing allows for functional MRI of human brain activation on a routine clinical instrument even at a low magnetic field strength of 1 T. The approach is feasible, sensitive, and – compared with data obtained at 3 T – reliable. This observation is in accordance with the few published studies performed at 1 T. Similar functional contrast, i.e., MRI signal changes in response to a functional challenge, may be obtained at different field strengths by adjusting the gradient echo time, while keeping the spatial resolution constant. The use of a suitable post-processing strategy may largely compensate for low SNR.

2. Diagnostic studies (neurosurgical planning and functional neuronavigation)

In Hungary, we was the first who uses fMRI in a clinical routine; and 114 sessions with 48 patients examined and operated based on the results surely prove, that (a) fMRI of clinically relevant paradigms with proper settings is easy to use, (b) it can be acquired and analyzed with good quality even at 1T (c) visualizing the eloquent areas with good accuracy, and (d) able to be applied for neurosurgical planning and functional neuronavigation. It can provide accurate and flexible real-time functional guidance for the neurosurgeon making other invasive and cost- and resource-demanding methods unnecessary. (e) Finally, as we accomplished the examinations on a clinical scanner widely available in Hungary; this method can be widely applied.

3. A novel group analysis

Experimental analyses involved fMRI examinations of eight subjects using SFO and IWG paradigms at 3 T. Preprocessing included motion correction, normalization to MNI space and spatial filtering. Originated from TTC, at first we calculated the individual correlation

coefficient (CC) maps. Based on the distribution of the CC-values representing all voxels of all subjects, we determined the two CC thresholds referring to the whole group, for the $p = 0.0001$ and $p = 0.05$ respectively. Then these thresholds were applied onto the group CC maps achieved in two different ways: by a selection of either the maximum CC value (MAX) or by calculating a mean CC value (MEAN) for each individual voxel.

While the results for the TTC MAX approach were very similar to those obtained from a standard SPM analysis, the TTC MEAN approach turned out to be more conservative emphasizing voxels activated in most rather than in only a few subjects.

The proposed TTC group analysis for fMRI appears to be advantageous in several respects: (a) it is simple, transparent, and fast, (b) it is robust with respect to physiologic variability by estimating the noise distribution and respective thresholds from the actual experiment, and (c) it may minimize the problem of false positive activations by combining two thresholds for the identification of activations and by taking the mean of individual CC values for the respective group analysis.

4. Visualizing epileptic activity

A 20-year-old female patient was examined with right-sided mouth cloni. Structural images showed no epileptogenic lesion. Ictal-fMRI examination was conducted on a clinical scanner operating at 1T field strength. Analysis was accomplished with TTC using internal hemodynamic reference function acquired from motor area responsible for mouth movement (i.e. cloni). Reference curve was shifted from scan-to-scan to determine areas activated at a given time point. Then, signal alterations of these areas were analyzed to determine the start of their activations. Activation times were visualized using a color-coded “Lag-map”.

(a) The first activation occurred more than a minute before the clinical onset in the left insular cortex. (b) Motor area responsible for mouth movements showed five-second-long pre-ictal

phase. Additional activations were found in the ipsilateral basal ganglia and the ipsilateral cerebrum and cerebellum with different onsets.

To our knowledge, ours is the first study that describes, simultaneously in time and space, whole-brain haemodynamic changes during an epileptic seizure. Our observations might contribute to a better understanding of the pathophysiology of seizure spread. Moreover, the identification of the putative seizure-onset zone can be crucial for presurgical evaluation of epilepsy patients. In the case presented, the putative seizure-onset zone could have been validated by successful surgery. However, the frequency and severity of the patient's seizures have been considerably reduced, and she refused to undergo further invasive investigations.

5. Combining with DTI-FT

Patient after a severe traumatic brain injury was examined with fMRI and DTI at 1T field strength. DTI measurement – for the sake of comparison – was accomplished on a healthy subject. Analysis was done with TTC (fMRI) and DTIstudio (DTI).

Result of DTI analysis (a) visualized neural tracts; (b) confirmed damages of neural tracts of the patient in concordance with clinical examinations; (c) provided explanation to fMRI results.

DTI-FT even at low field can *in vivo* visualize neural tracts adequately mirroring their actual position and status thus improving the diagnosis of e.g. TBI. It is important to notice, that our application is just one of the many possible ones. This method can provide useful information about other pathologies affecting white matter (brain tumor, multiple sclerosis, dyslexia, schizophrenia etc.). Finally, as we accomplished the examinations on a clinical scanner widely available in Hungary; this method can be widely applied.

6. Recording neural activities by means of SPECT using modified SISCOM-analysis

Our patient underwent DBS of the left globus pallidus interna (GPi) due to secondary hemidystonia developed after perinatal brain injury. Preoperatively, functional MRI (fMRI) was conducted to determine her speech dominance. Postoperatively, structural MR examination was used to localize the electrodes. During testing different settings of parameters for DBS, we accidentally find a stimulation setting (steady-state) for developing reproducible déjà vu, thus obtaining the possibility to study it in more detail; in informed agreement with the patient. SPECT study was performed one month postoperatively to visualize brain activity during experiencing déjá vu using a modified SISCOM analysis applying two thresholds similar to TTC.

Preoperative fMRI revealed right-sided speech-dominance. The postoperative MRI demonstrated that the stimulating electrode passed through the GPi, but did not hit the mesiotemporal structures. During steady-state the patient experienced reproducible déjà vu 3-5 times hourly, but only when her eyes were open and she was addressed with questions. Déjà vu lasted for a few seconds and were not accompanied by any hallucinations or illusions. SISCOM analysis demonstrated the hyperperfusion of hippocampus, parahipoccampal gyrus and cerebellum on the right side, and cerebellum, insula and middle temporal gyrus on the left. The hypoperfusion of bilateral sensomotor and other frontal and parietal lobe areas was observed.

To our knowledge, ours is the first study that describes, simultaneously in time and space, whole-brain hemodynamic changes during DV. Our observation is in good concordance with those in literature. Summing up our results and theories with those of others, we may assume that certain constellation (e.g. DBS wit specific electrode localizations and stimulation parameters, individual neuroanatomy and certain cognitive state) is needed to be able to elicit DV.

List of own publications, presentations and posters

(cumulative IF: publications: 26.17; abstracts: 15.21)

The thesis is based on the following publications:

Auer T, Schwarcz A, Janszky J, Horváth Zs, Kosztolányi P, Dóczi T. [Application of functional MR-images acquired at low field in planning of neurosurgical operation close to an eloquent brain area] Ideggyogy Sz. 2007;60:35-40.

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