Health Sciences Doctoral (PhD) School

Faculty of Health Sciences

University of Pécs

Head of the Doctoral School: Prof. JÓZSEF BÓDIS MD

Head of the Programme: Prof. ISTVÁN KISS MD

Supervisor in the Doctoral School: Dr. ÁRPÁD KOVÁCS PHD, MED HABIL

The integration of modern functional cross-sectional imaging with 3D based radiotherapy of tumors of the central nervous system

- Methodology and Validation -

PhD Thesis

Csaba Vandulek

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1. Introduction

The continuous development of magnetic resonance imaging (MRI) has paved the way for the development of complex functional MRI (fMRI) which can localize functional areas and activations of the functional areas within the central nervous system (CNS). The use of fMRI data to assist neurosurgery has become routine in clinical ractice today. Likewise, fMRI may prove to be useful to assist oncoradiology whereby fMRI data can be used to guide and optimize radiotherapy treatment plans in the case of intracranial tumors.

Treatment of the planned target volume (PTV) with the right dose is critical in modern 3D radiotherapy, however, the sparing of normal tissue and their structural and functional integrity is equally as important. This is even more critical in the case of the CNS where the majority of brain tissue is functionally important, thus damage to any area of the brain tissue will impair the quality of the patients' life. Consequently, the protection of normal brain tissue is important in this respect.

FMRI examinations can help map the respective functional areas of the brain in order to provide valuable information in the treatment planning. The integration of complex fMRI data with the treatment planning is only possible if the data is exempt from motion artefacts, and if the acquired functional maps are precise. At present, there is very limited experience of the integration of fMRI data with complex oncological patient care; currently it is not a routine procedure in clinical practice.

The goal of this project was to prepare and found the basis of clinical fMRI examinations at the Health Center of Kaposvár University in respect to oncoradiology. This complex project consisted of gaining experience of the use of a dedicated fMRI hardware/software system, a feasibility study, testing the fMRI protocol on volunteers prior to implementing it in clinical practice, performing volumetric analysis of the functional areas and testing the reproducibility of it, development of the clinical fMRI protocol based on the results of the study. The project aimed to assess the volunteers'

anxiety, tolerance, fatigue and further subjective aspects in order to allow optimization of the future clinical fMRI protocol and the patient preparation phase.

Functional magnetic resonance imaging

Visualization of the various stimuli and the resulting changes of activation is made possible with functional brain imaging methods which allow detailed study of the functional processes of the brain. FMRI allows the identification of functionally active areas of the brain and the study of the changes in activation due to various stimulations of the nervous system. Its main advantage is the fact that it is non-invasive, furthermore it provides reasonable spatial resolution and good temporal resolution.

MRI related anxiety

Generally speaking a patient in the healthcare system encounters a stress situation which increases the patients' level of anxiety. The level and intensity of anxiety of the patient depends on how the patient appreciates the encountered stress. The MRI environment and the experience of the examination may further impact the tension experienced by the patient leading to unpleasant and negative cognitive feelings.

If the patients' level of anxiety cannot be reduced, the patient will then be incapable of staying motionless during the MRI examination. This in turn would have a negative impact on the quality of the acquired images which can be detrimental in the case of MRI. Patient movement during an MRI examination may lead to blurry images, blurry anatomical structures or even ghosting artefacts. Such technical issues may seriously impair the reading of the images by the radiologists. In such cases, the examinations may need to be repeated or alternative types of examinations may need to be considered.

Studies of MRI related anxiety are rare and limited in their outcomes. Some studies have suggested a relationship between MRI related anxiety and patient discomfort. Other studies have shown the manifestation of anxiety in the majority of oncology patients due to the overall increase of the level of anxiety and distress of such patients. This increased level of anxiety results in poor image quality and a compromise of the success of the fMRI examinations in the case of patients with intracranial tumors.

2. Aims

I. To learn and gain experience of the use of a new dedicated fMRI system.
II. To assess the level of tolerance, fatigue, comfort and further subjective aspects of an fMRI examination on healthy volunteers.
III. To assess the user-friendliness of the fMRI system.
IV. To assess the volunteers' anxiety in regards to the fMRI examination and develop techniques to reduce anxiety.
V. To perform volumetric measurements of complex fMRI measurements and assess the reproducibility of the volumetric measurements.
VI. To prepare the implementation of complex fMRI examinations within oncoradiology.

3. Materials and Methods

Study subjects

Altogether 9 female and 9 male students of the Faculty of Health Sciences, University of Pécs, participated in the study. Following an extensive MR safety screening process all study subjects provided their written consent to participate in the study.

MRI equipment

The examinations were performed on a 1.5T Siemens Magnetom Avanto® MRI system. The implementation of the fMRI paradigms was with the nordicAktiva fMRI software and hardware system. The nordicICE® software was used to post process the fMRI data.

Preparation of the volunteers for the fMRI examination

Preparation of the volunteers was done on an individual basis. Prior to each examination, the radiographers provided detailed information of the paradigms, the stimuli and the expectations from the volunteers. The volunteers had a chance to practice the paradigm prior to real data collection.

Psychological preparation of the volunteers

The volunteers underwent a special preparation phase in order to reduce their level of anxiety. Prior to patient positioning, psychological support was provided in order to

help the volunteers stay relaxed and focused on the fMRI paradigms. The psychological preparation consisted of two parts. First, in order to maintain a general well-being and comfort during the examination, the volunteers were reassured that they were not experimental objects, but partners in the research. Secondly, they undertook a short 10 minute long autogenic training to help them stay in a relaxed state and focused during the execution of the paradigms.

STAI questionnaires

The Spielberger State Trait Anxiety Test (STAI-S; STAI-T), validated for Hungary, was used to assess the volunteers' general anxiety level in comparison with their anxiety of the fMRI examination. The STAI-T and STAI-S questionnaires were filled out prior to the psychological preparation phase. The STAI-S questionnaire was filled out straight again following the end of the fMRI examination in order to assess changes in the level of state anxiety.

Pre- and Post fMRI questionnaires

Each volunteer had to fill out a pre-fMRI (medical case-history) and a post-fMRI questionnaire (experiences related to the fMRI examination).

fMRI paradigms

Altogether six different paradigms were used in the project. The paradigms were: checkerboard (visual), word generation, word comprehension, finger tapping memory, emotion; all of which used different visual and/or acoustic stimuli.

Volumetric analysis

The double-blind interobserver volumetric analysis was performed by two radiographers using the dedicated nordicICE® software.

4. Results

Areas of activation were observed in the case of all paradigms with the exception of the emotion paradigm. The image quality was good, there were no signs of motion or other artefacts in the fMRI measurements. Only 6 measurements had to be repeated out of the 108 BOLD fMRI measurements.

fMRI related subjective aspects

The total imaging time was between 49-65 (55±4 min) minutes. One volunteer considered the length of the examination as being short, one volunteer considered it to be long, whereas the rest of the volunteers considered it to be acceptable.

Four volunteers experienced numbness and stiffness arising from the patient positioning and from creases in the sheets on the examination table. One volunteer complained of discomfort arising from the headphones. Two volunteers experienced headaches during the examination. Altogether 5 instances of fatigue were registered (these all occurred towards the end of the examination). The majority of the volunteers found the examination to be comfortable or acceptable, whereas only three volunteers found it to be uncomfortable.

The majority of the volunteers considered he fMRI hardware and techniques to be user-friendly, whereas one volunteer considered it to be awkward and difficult to use.

Result of the STAI tests

The STAI test showed the presence of a general level of anxiety amongst the volunteers (STAI-T: 41,67±8,96). The results also showed that the level of state anxiety was high prior to the fMRI examination (STAI-S pre-fMRI: 34,78±9,79). A significant difference between the volunteers' trait anxiety and pre-fMRI anxiety was confirmed; the volunteers' level of trait anxiety was higher compared to the level of pre-fMRI state anxiety ($p<0,01$). The volunteers' level of post-fMRI anxiety (STAI-S post-fMRI: 28,83±4,99) was lower compared to the level measured pre-fMRI (STAI-S pre-fMRI: 34,78±9,79) ($p<0,01$). Linear correlation was observed between the levels of trait anxiety

and pre-fMRI anxiety (r^2= 0.5733). Linear correlation was also observed between the levels of trait anxiety and post-fMRI anxiety (r^2=0.4765).

No significant gender difference was observed in the case of trait anxiety (p=0,801). Likewise, no significant gender difference was observed in the case of pre- and post fMRI state anxiety (p=0,881;p=0,438).

Volumetric analysis

Volumetric analysis of the activation areas was performed by two radiographers. The emotional paradigm did not provide useful data, therefore volumetric analysis was not performed in the case of the paradigm. Correlation was experienced between the data provided by the two radiographers in respect to the other five paradigms.

5. Discussion and Conclusion

fMRI related subjective aspects

Fatigue was registered near the end of the fMRI examination in 5 of the 18 volunteers. The length of the examination (55±4 min) can be considered to be acceptable under normal conditions in the case of healthy volunteers, however, the length of such complex fMRI examinations should be reduced in clinical practice.

Oncology patients in a progressive stage are usually in a poor physical condition with poor mental concentration capabilities in comparison with healthy people. Therefore, it is suggested to revise the tested fMRI protocol in order to optimize it on clinical patients for clinical implementation.

The volunteers tolerated the fMRI examination well. The volunteers rated the examination as being comfortable, nonetheless, further patient positioning and comfort providing accessories (eg.: pillows, cushions, blankets) should be provided when examining oncology patients who are generally in a poor physical condition following surgery or chemotherapy. It would be expected that such patients have a lower level of

tolerance of compromised space, lengthy examination times and numbness in comparison with healthy volunteers.

Patient preparation has to be a priority in the case of such complex examinations. Dedicated professional preparation will in turn result in less complications and disturbances during the examination itself and more focused execution of the tasks by the patients during the paradigms. A dedicated preparation phase should include an exchange of detailed information of the paradigms, an opportunity to practice certain tasks (paradigms), and in addition, professional support from a psychologist providing techniques for the patients to help them stay relaxed and focused during the examination. Such a dedicated patient preparation phase would be expected to contribute to the execution of good fMRI examinations and the reduction of paradigm reputation or even aborted examinations.

The volunteers considered the fMRI equipment to be user-friendly and tolerable. The volunteers were grateful of the special patient preparation they encountered and viewed it as being helpful. They also highlighted the special psychological support prior to the examination as helping them stay calm and relaxed with the ability to concentrate on the paradigms. Nevertheless, the registered fatigue and discomfort suggests the need to reconsider and further optimize the protocol prior to clinical implementation.

Anxiety

Assessment of the volunteers' state anxiety showed that the volunteers' level of state anxiety decreased during the fMRI examination when compared with the pre-fMRI level, however, there was no significant gender difference observed. Similarly to studies in other clinical areas, the significant decrease of the state anxiety is most likely attributed to the careful and attentive patient preparation including the psychological support. The correlation (r^2= 0,5733) between the trait anxiety and the pre-fMRI level of anxiety suggests that the higher the level of trait anxiety of a volunteer, the higher the volunteers' level of state anxiety. Similar relation (r^2=0,4765) was observed between the trait anxiety and the level of post-fMRI anxiety.

Volumetric Analysis

Correlation was observed between the results of the radiographers in the case of all five paradigms. It is important to state that only small differences were noted between the independently measured activation volumes. This suggests that the volumetric measurements can be safely performed after careful choice of the optimal level of significance. The optimal level of significance reduces activation noise allowing the identification of the real activation signal.

Technical aspects

It is important to emphasis that fMRI examinations are complex advanced MRI examinations which require special attention compared with the execution of routine examinations. Therefore, it is mandatory that the radiographers are well trained with not only having experience in performing such advanced examinations, but in image processing, post processing as well as in using the fMRI software and hardware. There was no study found in peer literature focusing on the radiographers' advanced role when performing fMRI examinations, nevertheless, based on this study it can be stated that the well trained and experienced radiographers contributed greatly to the success of the complex fMRI examination.

Of the 108 paradigms there was only 6 cases when a paradigm had to be repeated. The acquired MRI images were of good quality and free of any motion artefacts. The only paradigm which did not bring good results was the emotion paradigm, but this had nothing to do with the radiographers, instead it is attributed to the set of images used in this paradigm to evoke feelings. This study aimed to provide an opportunity for the well trained research team (including the radiographers) to gain experience in performing complex fMRI examinations on healthy volunteers. This in turn would help the team to be able to perform complex clinical fMRI examinations of high quality on oncology patients.

Conclusion

The objective of this study was to prepare the integration of clinical fMRI examinations into modern 3D based radiotherapy treatment planning. The feasibility of

the complex fMRI protocol was studied on healthy volunteers in respect to fMRI related tolerance, fatigue, comfort and user-friendliness of the dedicated fMRI equipment. Furthermore, it studied the volunteers' level of fMRI related anxiety and the opportunity to reduce their level of anxiety. The study also aimed to allow the participating radiographers to learn and gain experience in performing such complex fMRI examinations using dedicated fMRI software and hardware. This phase included the dedicated patient preparation process, use of the fMRI software and hardware, the execution of the fMRI measurements and the post-processing of the acquired data.

The results of the study and the feedback of the radiographers was used to optimize the fMRI protocol and the patient preparation phase prior to clinical implementation. The fMRI working group is currently working with clinical patients and have already performed fMRI examinations of good quality on 17 patients with brain tumors. The results so far have demonstrated that the radiotherapy treatment has an effect on the functionally active MRI signals. Functionally active areas located in the area of high dose (>40 Gy) relocated to low dose areas (<40 Gy), furthermore, secondary motor activation areas also appear.

6. New Scientific Results

I. **The study of complex fMRI related tolerance, fatigue and comfort on healthy volunteers.**

II. **The study of fMRI related anxiety.**

III. **The implementation of psychological support to reduce the level of anxiety leading to the execution of successful fMRI measurements.**

IV. **Double-blind interobserver analysis of the volumetric measurements of fMRI activation data and the assessment of the reproducibility of the volumetric measurements**

V. **Development of a complex fMRI protocol to be implemented in complex oncoradiology in the case of patients with brain tumors.**

7. Key Publications

Publications in English language:

Kovács Á., Emri M., Opposits G., Spisák T., **Vandulek Cs.**, Glavák Cs., Szalai Z., Biró G., Bajzik G., Repa I.: Changes in functional MRI signals after 3D based radiotherapy of glioblastoma multiforme. *Journal Of Neuro-Oncology* 2015;125(1): pp.157-166. ***IF$_{2014}$: 3.070***

Vandulek Cs., Donkó T., Illés A., Emri M., Opposits G., Repa I., Kovács Á.: Anxiety management and functional magnetic resonance imaging - should it be a priority? *Ideggyógyászati Szemle / Clinical Neuroscience* 2015;68(9-10): pp.318-324. ***IF$_{2014}$: 0.386***

Vandulek Cs., Somogyi E., Repa K., Bíró G., Réfi L.: Exploring fMRI: tolerance, fatigue, comfort, user-friendliness. *Hold Pusten* 2015;42 (2): pp. 27-29.

Kovács Á., Tóth L., Glavák Cs., Lakosi F., Hadjiev J., Bajzik G., **Vandulek Cs**., Repa I.: Integrating functional MRI information into radiotherapy planning of CNS tumors-early experiences. *Pathology And Oncology Research* 2011;17 (2): pp. 207-217. ***IF$_{2011}$: 1.366***

Kovács Á., Tóth L., Glavák Cs., Liposits G., Hadjiev J., Antal G., Emri M., **Vandulek Cs**., Repa I.: Integrating functional MRI information into conventional 3D radiotherapy planning of CNS tumors, is it worth it? *Journal Of Neuro-Oncology* 2011;105(3): pp. 629-637. ***IF$_{2011}$: 3.214***

10.1.1 Az értekezés alapjául szolgáló közlemények magyar nyelven

Vandulek Cs.: Funkcionális mágneses rezonancia vizsgálatok radiográfus hallgatókon - első eredmények. *Egészség-Akadémia* 2014;5(1): pp. 17-24.

Publications in Hungarian language

Kovács Á., Emri M., **Vandulek Cs**., Glavák Cs., Szalai Z., Biró G., Bajzik G., Repa I.: fMRI signal changes in the central nervous system after 3D based radiotherapy. *Insights Into Imaging* 6:(1 Suppl.) Paper B-0657. 1 p. (2015), ECR 2015 Book of Abstracts - B - Scientific Sessions and Late-Breaking Clinical Trials.

Kovács Á., Miklós E., Opposits G., Spisák T., **Vandulek Cs**., Glavák Cs., Bajzik G., Repa I.: Functional-MRI signal changes following 3D conformal radiotherapy of GBM patients. Early intra-observer variability results. *Radiotherapy And Oncology* 111:(Suppl. 1) p. 550. (2014) European Society for Radiotherapy & Oncology. Wien, Ausztria: 2014.04.04 -2014.04.08.

Vandulek Cs., Biró G., Réfi L., Tóth L., Emri M., Repa I., Kovács Á.: A study of the psychological distress of fMRI volunteers. *Insights Into Imaging* 5:(Suppl. 1) p. B195. (2014) European Congress of Radiology. Wien, Ausztria: 2014.03.06 -2014.03.10.

Kovács Á., Tóth L., Glavák Cs., Lakosi F., Hadjiev J., Bajzik G., **Vandulek Cs**., Repa I.: Integrating functional MRI information into radiotherapy planning of CNS tumors. *Radiotherapy And Oncology* 96:(Suppl. 1) p. 263. (2010) 29th Congress of European Society for Therapeutic Radiology and Oncology. Barcelona, Spanyolország: 2010.09.12 -2010.09.16.