

Study of Brain Activation in Small Animals using PET/MR Imaging

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Introduction:

Combined functional imaging, using information gathered by multiple modalities such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) opens new horizons in medical research. In this study we present two novelties, so far not shown in small animal imaging. By sequential PET and MR imaging we were able to study and compare brain activation in animals using [¹⁵O]H₂O PET and BOLD fMRI. In addition we were able to obtain *in vivo* BOLD data inside a MR compatible small animal PET-Insert [1], allowing future simultaneous PET/MR studies.

Material and Methods:

The studies focusing on a comparison between PET and BOLD fMRI brain activation were performed on a small animal PET scanner and a 7 T small animal MRI system, using male Lewis rats (n=6), average weight ca. 350 g. Animals were anesthetized using 1.5 % Isoflurane in air, and placed on a multimodality animal bed with stereotactic fixation. The body temperature of the rats was stabilized at (37±1) °C; physiologic parameters (e.g. respiration rate) were monitored. Stimulation of the left vibrissae was performed for PET as well as MR activation measurements.

To study PET brain activation, the perfusion tracer [¹⁵O]H₂O (T_{1/2}=122 s) was used, allowing to study multiple activation and baseline conditions within the same scanning session compared to long half life tracers such as [¹⁸F]FDG (T_{1/2}=110 min) which would require a long waiting time between activation and baseline conditions. A total of eight [¹⁵O]H₂O *i.v.* infusions (164 MBq) were performed in each animal. During every injection a 300s dynamic PET scan was started and either the animal was stimulated during the scan or a baseline was acquired, mimicking a fMRI block paradigm. Sequential BOLD imaging using a GRE EPI sequence (TR=2000 ms, TE=18 ms, matrix size: 64x64x8, voxel size: 0.5x0.5x1.0 mm³) and the same stimulation as for the PET acquisitions was performed within the same imaging session. Moreover also BOLD brain activation experiments were conducted using the above mentioned stimulation paradigm inside a small animal PET-Insert, allowing future simultaneous PET/MR acquisitions.

PET images were realigned and resliced, co registered and warped to a common [¹⁵O]H₂O PET rat brain atlas (constructed from the PET/MR data of 15 animals), and subsequently normalized to an average brain perfusion of 100 ml/min/100g, to prevent bias by physiological or injection fluctuations. The PET data was then analyzed using a subtraction analysis (activation-rest), as well as a statistical analysis on a group level (SPM8, Wellcome Trust Centre for NeuroImaging, London, UK).

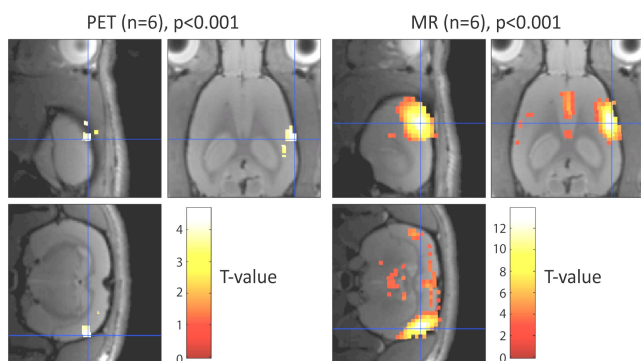


Figure 1: Comparison between PET and MR activation maps on a group level. A higher amount of activated voxels and significance level is observed using BOLD fMRI compared with PET. A difference between the peak activation centers between PET and MRI could also be observed, indicating a different physiological origin of the studied signal.

For the MR data, similar preprocessing steps were performed, including coregistration and warping to the same atlas as the PET data. MR functional activation maps were obtained using the general linear model. Special care was taken in constructing the matching [¹⁵O]H₂O PET/MR atlas and in the assurance of the coregistration process of the imaging data to this atlas, resulting in a coregistration accuracy of <1 mm found by visual inspection. Comparison of activation levels as well as locations between PET and MR measurements were performed.

Results:

A clear activation signal in the rat primary somatosensory barrel field cortex (S1BF) could be observed using [¹⁵O]H₂O PET and BOLD fMRI. The activated areas were in accordance to the expected region based on the Paxinos rat brain atlas. In PET a statistical significant (P<0.01) average increase of cortex perfusion on the contralateral side of (26±20) % compared to the ipsilateral side of (-4±22) % was observed. The average BOLD signal change in these regions was in the range of (1.5±0.7) %. PET as well as MR group level analysis (n=6) of the data show highly significant activations (P<0.001 uncorrected) in the S1BF (Figure 1). At this threshold the number of activated voxel in PET (31 voxel) is much smaller compared to fMRI (696 voxel). Nevertheless both, the PET as well as the fMRI activations are highly significant (P<0.001 corrected) on a cluster level. A spatial mismatch of 2 mm between the peak activations of the PET and fMRI was found. Moreover brain activation in the barrel field region could also be observed *in vivo* using BOLD fMRI inside a PET-Insert.

Discussion and Conclusions:

Measuring brain activation using [¹⁵O]H₂O PET techniques in rats was to our knowledge not demonstrated so far. The comparison of the PET to the fMRI brain activation yields qualitatively the same results, however even giving the higher [¹⁵O]H₂O PET signal change during activation compared to BOLD fMRI the PET method shows a lower number of activated voxels at a given statistical threshold. This can be explained to some extent by the limited number of acquired baseline and activation image sets of the PET method, compared to the BOLD technique. The spatial mismatch of 2 mm between PET and MR technique indicates a basic difference between the origins of the measured perfusion PET signal, which originates more from the brain parenchyma and capillary bed, whereas the GRE BOLD response is more sensitive to changes in the draining veins, supported by previous MR only studies [2, 3]. However care must be taken, since statistical activation maps are compared, which might differ from contrast images. The reduced number of activated voxels in the PET technique could therefore also be contributed to some extent to a more spatial specific localization of the activation areas. In addition the ability to perform BOLD fMRI brain activation experiments inside a PET-Insert, as demonstrated for the first time *in vivo* in small animals by our group, opens the field for further experiments using the high sensitivity of PET, e.g. for tracing neurotransmitters, and applying at the same time advanced MR techniques such as BOLD to study the basics of brain functionality.

References:

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