Simultaneous small animal PET/MR in activated and resting state reveals multiple brain networks

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Introduction:

The study of brain function in small animals as well as humans using the fMRI BOLD effect is of utmost interest for a great variety of neurological research fields. Little is known about the correlation of the BOLD effect with other functional brain imaging techniques such as PET. Especially the variety of confounding factors such as subject motion between scans makes such comparisons difficult. Here we compare for the first time, simultaneously acquired fMRI and PET data of brain networks involved in activated as well as resting state. We show that PET/MR functional data offers complementarities allowing studying multiple brain networks.

Material and Methods:

PET/MR device: A small animal PET insert, constructed by our group, consisting of 16 circularly arranged detector cassettes was used in this study. Each cassette houses three 3x3 Avalanche Photodiode arrays, coupled to a 15x15 LSO crystal (single crystal size 1.5x1.5x10mm³). The PET insert is installed inside the 20cm diameter gradient system of a 7T small animal MR scanner (Bruker/Siemens ClinScan). A linear polarized coil inside the PET insert is used for signal transmission, a local brain coil for reception.

Simultaneous PET/MR imaging: A total of eight, male Lewis rats (389±29g) were studied. Animals were anesthetized using 1.0% of isoflurane in air. The animals were placed on a temperature-stabilized bed (37.0±1°C) inside the PET/MR system. Simultaneously with an *i.v.* injection of 39±3MBq of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG, $t_{1/2}$=120min) a 60min PET scan, as well as a 45min permanent stimulation (3mA, 3Hz) of the left vibrissae were started. During the PET acquisition, anatomical MR data as well as a 15min resting state fMRI (rsfMRI) scan (EPI GE, TR=3000ms, TE=18ms, 64x64 matrix size, voxel size: 0.5x0.5x1.0mm^3, 18 slices) were recorded. The rsfMRI data was either acquired without any stimulation (i.e. true rsfMRI) or with a permanent stimulus applied (perturbed rsfMRI). In the last 15 minutes of the experiment a block design fMRI experiment (EPI GE, TR=2000ms, TE=18ms, 64x64 matrix, voxel size: 0.5x0.5x1.0 mm^3, 8 slices) was performed. On the consecutive day the PET/MR experiment was repeated, however without the 45min stimulation during the PET scan. PET data were reconstructed dynamically using a FBP algorithm, as well as MR based PET attenuation correction. SPM was used for subsequent data processing. [^{18}F]FDG PET activation was determined by a paired t-test (8 pairs). A measure for the cerebral metabolic rate of glucose consumption (CMRGlc) was obtained by scaling standardized uptake values (SUV) in 1.5mm radius spheres around the peak PET activation areas to a resting brain CMRGlc of 28.1 µmol/100g/min. BOLD activation was determined by a GLM fit. rsfMRI and also PET dynamic datasets have been evaluated using an independent component analysis (group level ICA, 15 components for rsfMRI, 13 components for PET), to map default mode networks under resting as well as under permanent stimulation condition.

Results:

Figure 1 shows a comparison of significant ($p<0.01$) activations for three different center of slice positions, relative to the Bregma, obtained with simultaneous PET/MR. The fMRI BOLD activation (block paradigm) mainly shows areas in the contra lateral barrel field cortex (S1BF cl) as well as in the nucleus of the nucleus accumbens (NAcc) and the cingluate cortex (Cg 1/Cg 2) activated during whisker stimulation. [^{18}F]FDG PET revealed additional structures. Despite S1BF cl and NAc, especially the ectorhinal cortex (ECT) with the insular cortex, the caudate putamen with the basolateral amygdaloid nucleus (BLA cl and il) in connection with the and the ventral posteromedial thalamic nucleus (VPM) and the amgydala (Amyg.) showed increases in CMRGlc during stimulation in the order of 12 to 21% in a spherical ROIs around the peak activation (Table 1). Whole brain CMRGlc showed a tendency towards a higher CMRGlc (not significant). Deactivated areas ($p<0.01$), lower signal during stimulation compared with rest, have been found for fMRI BOLD in the motor cortex (M1 il, cl) as well as in the forelimb somatosensory cortex (S1FL) and small areas in S1BF il. No significant deactivations have been found for [^{18}F]FDG PET. ICA found for the rsfMRI data in the resting state (no permanent stimulation) a number of approximately 6 meaningful cortical circuits, including the motor cortex, somatosensory cortex, striatal areas (Figure 2). During permanent stimulation, these "default" mode networks relocated to slightly different positions, and showed a higher z-score. However a smaller number of meaningful circuits were detected during permanent stimulation. ICA of the PET data identified different networks, compared to the rsfMRI data, corresponding even in the resting state (no permanent stimulation) more closely with fMRI and PET activation maps.

CMRGlc [µmol/100g/min]	w Brain	S1BF cl	Ect	BLA cl	BLA il, VPM	Amyg.
rest	28.1±5.2	28.9±4.6	23.3±4.9	27.5±5.1	21.9±3.7	11.1±2.8
stim	30.7±3.4	32.4±3.5	27.1±3.4	30.7±3.8	25.8±4.4	13.3±2.7
%Change	9	12	16	12	18	21

Table 1: Changes of brain glucose metabolism during stimulation (n=8).

Discussion and Conclusions:

The fMRI and PET activation data showed some similarities in the somatosensory stimulation network (e.g. S1BF). However, additionally activated areas were found using [^{18}F]FDG PET. This can be explained by the different stimuli durations for the fMRI (5 blocks, each 30s) and PET (permanent 45min). The long duration of the per se non noxious stimulus during the PET scan, might evoke additional networks in the brain, known to be involved in pain processing. The tendency towards a higher whole brain CMRGlc during stimulation shows probably a risen level of awareness caused by the sensation. This is also reflected by the higher z-scores and the shift in the default mode networks identified in the rsfMRI data, were the permanent stimulation acts as a perturbation of the brain networks. The PET ICA data reveals an alteration in the default mode networks during stimulation, but particularly, shows different components not identified in the rsfMRI data. Therefore multiple metabolic networks and stages of brain activation can be revealed by simultaneous PET/MR imaging.

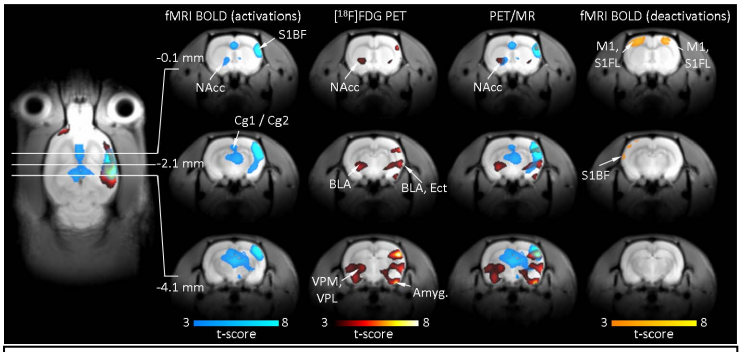

Figure 1: Significant (p>0.01) brain activation visualized by simultaneous fMRI/PET. fMRI shows activated areas mainly in the somatosensory cortex (S1BF), whereas PET shows additional brain networks, e.g. the amygdala involved in processing. Areas in the motor cortex are deactivated in fMRI during stimulation, these areas were not found to correspond with PET.

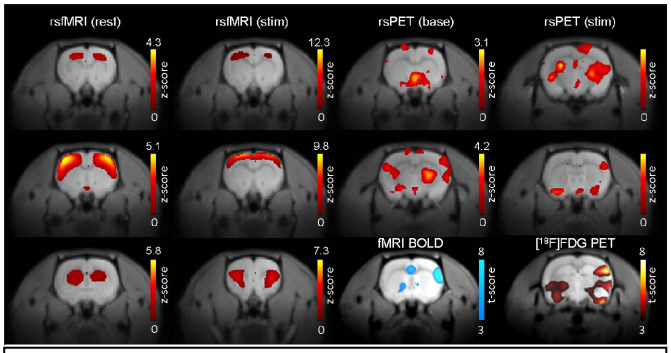

Figure 2: Group level default mode networks in the brain obtained via ICA. rsfMRI during rest and permanent stimulation shows networks in the motor cortex, somatosensory cortex and striatum. These do not correspond with the ICA of the PET data that is more closely to the areas obtained during the stimulation paradigm.