The potential of PET/MR for brain imaging

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Abstract

Introduction The completion of an integrated PET/MR prototype system for brain imaging is the latest step in the evolution of positron emission tomography. Early images with this new imaging system demonstrate that high-resolution multiparametric studies can be combined without significant loss of performance of either imaging modality. *Objective* This new technology will make fusion of morphological and biological information much easier, yield real-time assessment of complementary variables and will provide dynamic information for kinetic modelling. Simultaneous acquisition of various metabolic and functional parameters may open new insights into the organization of the brain and its changes in disease. *Discussion* A new field may open up for molecular and cellular imaging, where new targets – e.g. angiogenesis, gene transfer, function and migration of transplanted cells – can be imaged in the morphological context and within a functional environment. This application might have a special impact on the translation of treatment concepts from experimental models into clinical application. If the added value of the hybrid system for diagnosis and treatment monitoring is established, a cost-effective PET/MR combination might attain wider clinical application.

Keywords PET/MR · BrainPET · Image fusion · High-resolution biological imaging · Multi-parametric imaging · Gene transfer and expression · Cell function and migration

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Introduction

Since the first prototypes [1, 2] and the first commercial system [3], positron emission tomography (PET) has developed to multiring systems permitting high resolution and three-dimensional imaging of various physiological, functional and molecular targets. The first applications of PET were in brain research, and despite the many other diagnostic indications, particularly in oncology and cardiology, brain imaging remains a stronghold of PET.

Therefore, this discussion of perspectives of an integrated PET/MR system is focused on research applications in neuroscience to which the combination of PET and MRI may add further impetus. This perspective is in parts speculative and it does not include a discussion of the technical or methodological challenges of combined PET/MR imaging. These aspects are reviewed elsewhere in the articles of this supplement to EJNMMI.

Development of PET for brain imaging

The progress in image quality may be followed by metabolic images of glucose consumption in one volunteer acquired on several generation PET systems over the years. The first transaxial image (Fig. 1a) was acquired on a single hexagonal array, the ECAT PET, which covered only the cortical rim. Early PET images suffered from limited spatial resolution (approximately 15 mm), low sensitivity and insufficient attenuation and scatter correction [3, 4]. PET image quality improved with the four-ring PC-384 (Scanditronix) [5], which yielded seven simultaneous, partly overlapping transaxial images and that provided a spatial resolution of 8.4 mm FWHM across 12-mm slices (Fig. 1b) [6] and limited axial reconstruction (Fig. 2). Further improvements came with the

Fig. 1 Various PET systems over the years demonstrate improvement in image quality and spatial resolution. **a** ECAT II, spatial resolution 15 mm. **b** PC-384, FWHM 8.4 mm. **c** ECAT EXACT, FWHM 6.5–7 mm. **d** ECAT EXACT HR, FWHM 3.6–4.5 mm. **e**, **f** HRRT PET: **e** prototype; **f** final version (HRRT-FV), FWHM 2.3–3.2 mm. Images of glucose metabolism were acquired for 20 min of steady-state starting 30 min after tracer administration
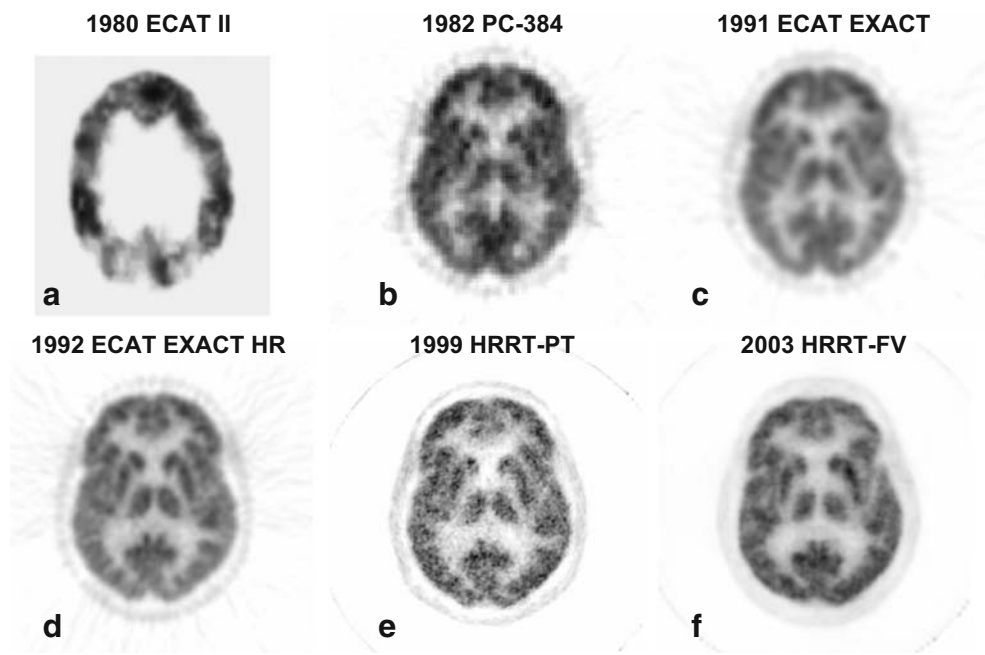

ECAT EXACT PET, which yielded 47 contiguous image planes with a spatial resolution of 6.5–7 mm and 5–8 mm in the transverse and axial directions, respectively (Fig. 2) [7]. For the first time the entire brain could be imaged in a single PET examination. The next generation PET system, the ECAT EXACT HR, provided further improvements of the spatial resolution (3.6 mm and 4.0 mm in the transverse and axial direction, respectively), sensitivity and image quality [8] (Figs. 1 and 2). With the dedicated high-resolution research tomograph (HRRT) PET image resolution improved to 2.3 mm and 2.5 mm in the transaxial and axial directions,

respectively, while sensitivity has increased to 4.3% [9, 10] (Figs. 1 and 2).

The most attractive feature of PET is the high sensitivity and specificity in detecting biochemical and molecular tracers, but it suffers from limited spatial resolution. Therefore, coregistration of PET images with morphological imaging modalities such as CT and MRI has been studied [11, 12], but is not yet in routine clinical use. Research applications of image fusion software have also been challenged by, for example, mapping of molecular and genetic activities to certain cortical areas.

Fig. 2 Coronal views of glucose consumption of the brain in a volunteer acquired with various PET systems over the years demonstrate improvement in axial resolution due to decreased slice thickness and advances in image reconstruction. **a** ECAT II (1980) was a single-ring camera; axial reconstruction was therefore not feasible. **b** PC-384, slice thickness 12 mm. **c** ECAT EXACT, axial FWHM 5–8 mm. **d** ECAT EXACT HR, axial FWHM 4.0–6.7 mm. **e**, **f** HRRT PET: **e** prototype; **f** final version (HRRT-FV), axial FWHM 2.5–3.4 mm
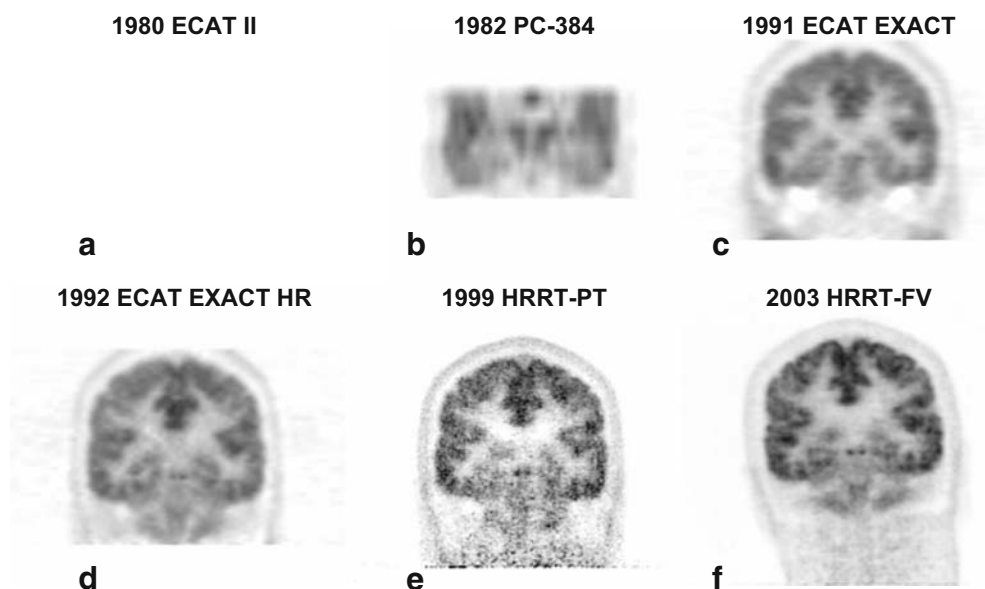
The integration of PET and CT into one imaging system permitting a simple overlay of sequentially acquired images has been a great success in clinical diagnosis [13]. However, because of the limited soft-tissue specificity of CT, this integrated system is not of great value for brain imaging. The installation of a HRRT PET system adjacent to a high-field 7T MRI system allows the utilization of high sensitivity molecular/biochemical and high-resolution anatomical imaging for brain research [14]. However, this system is not integrated and therefore does not permit simultaneous PET and MR data acquisition. For that purpose an integrated PET/MR system is required, which would permit the simultaneous coregistration of various MR and PET procedures. Schmand et al. demonstrated for the first time that simultaneous PET and MR data acquisition is feasible with an integrated PET/MR tomograph [15]. Figure 3 shows the first simultaneously acquired MR and PET images [16] in a volunteer and demonstrates the feasibility of combined MR and PET data acquisition without significant interference between the two modalities. Conventional MR imaging on a 3-T MR tomograph was performed using a T2-weighted turbo-spin

echo sequence, a fluid attenuated inversion recovery sequence and a 3-D T1-weighted fast low-angle shot sequence. Additionally, diffusion-weighted imaging, time-of-flight MR angiography (MRA) and proton MR spectroscopy were performed during the acquisition of the PET data. For PET imaging 370 MBq of ^{18}F-fluorodeoxy-D-glucose was intravenously injected and the activity in the head was accumulated over 40 min, starting 20 min after tracer injection. PET images were reconstructed using a 3D-OSEM algorithm following scatter, randoms and attenuation correction. The resolution of the reconstructed images was 2.5 mm FWHM at the centre and 4.5 mm at 10 cm off-axis with a sensitivity of 5.6%. Overall, the quality of the images was comparable to that of the corresponding stand-alone PET and MRI systems [16].

Advantages of an integrated PET/MR system for image fusion

With the installation of PET/MR systems in a clinical environment, this integrated imaging modality, which is

Fig. 3 PET/MR imaging with BrainPET system in a volunteer. Three representative orthogonal slices demonstrate the alignment of anatomic (3-D T1-weighted MRI) and metabolic images (FDG-PET). Asymmetries in the frontotemporal cortex are related to small white matter hyperintensities
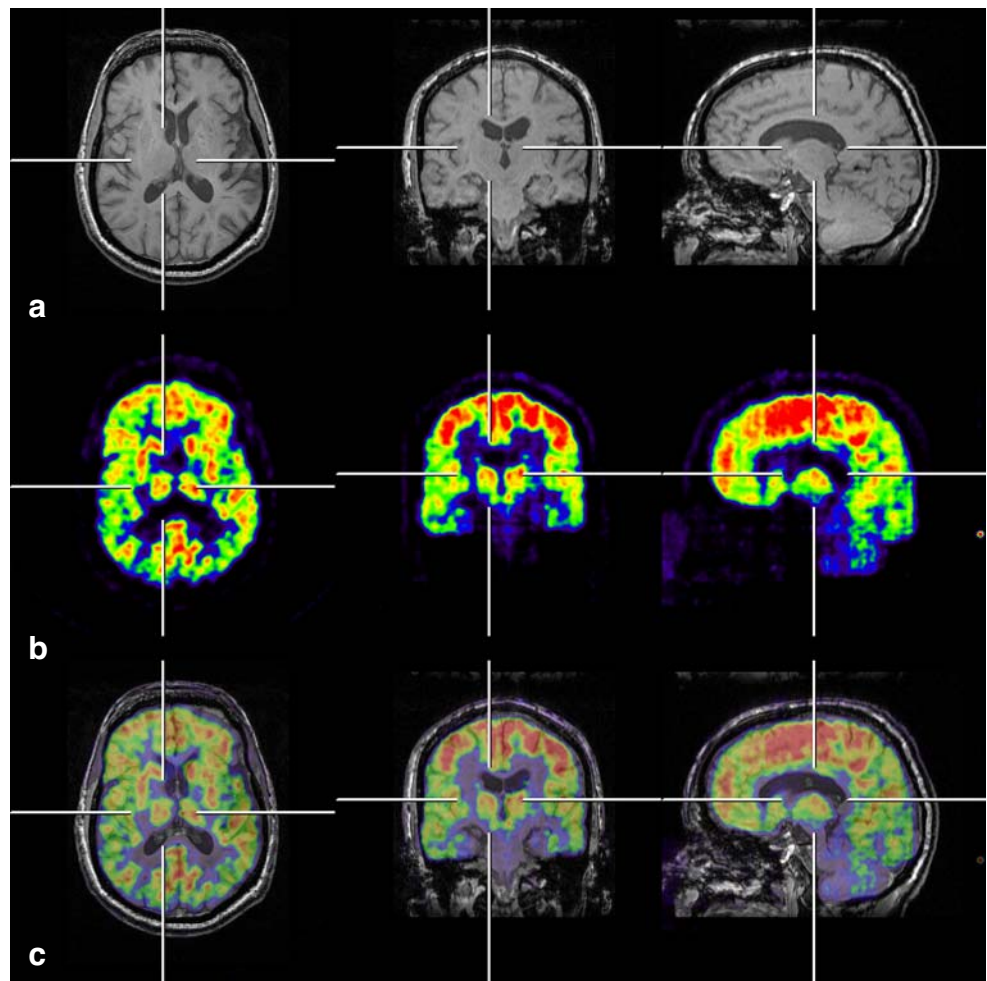
already utilized in preclinical research already is on the verge of being applied to the clinical neurosciences [17, 18]. An integrated PET/MRI system will permit the simultaneous acquisition of several parameters (Table 1). Quantitative values from PET (some in the picomolar range) of a large number of biological parameters are complemented by the high-resolution information provided by MRI (in the micromolar range) to yield complementary information of previously unexpected variability.

The combination of imaging modalities for high sensitivity and high resolution with the additional advantage of utilizing dynamic acquisition procedures appears very appealing for a variety of clinical and research applications. Recently, PET data and MRI data have been retrospectively combined for detection and staging of gliomas [19, 20] as well as for identification of areas with critical neurofunction in the vicinity of tumours, which is important for planning surgery [21]. Image fusion has gained a place in the early diagnosis of dementia and mild cognitive impairment [22] and degenerative disorders, e.g. cerebral atrophy and Huntington chorea. Image fusion is of clinical value in the detection of epileptic foci accessible for surgery [23] and for the identification of metabolic activity, transmitter concentration and enzyme expression in small brain structures [24]. In experimental focal brain ischaemia and ischaemic stroke, coregistration of regional values for cerebral blood flow, oxygen utilization and glucose metabolism on early and late MRI has permitted the differentiation of irreversibly damaged areas and functionally impaired but morphologically preserved areas, thus affecting treatment strategies [25].

Table 1 Assessment of biological properties by MRI and PET

MRI	PET
Morphology	Flow ($H_2^{15}O$)
Water motion in tissue (DWI)	Metabolism (FDG)
Vascular anatomy (MRA)	Blood volume ($C^{15}O$)
Perfusion (PWI, DCE-MRI)	Oxygen consumption (^{15}O)
Tissue metabolites (MRS for ^1H, ^{13}C, ^{23}Na, ^{31}P)	Vascular permeability (labelled AA)
Functional activation (fMRI)	Nucleic acid synthesis (FLT)
Cerebral fibre tracts (DTI)	Transmitters (e.g. DOPA)
Oxygen consumption (^{17}O)	Receptors (e.g. raclopride)
Migration of cells (Fe labelling)	Enzymatic activity (e.g. MP4A)
	Angiogenesis (e.g. ^{18}F-RGB)
	Distribution and kinetics of tracers and drugs (labelled compounds)
	Enzymatic activity in transfected cells

Real-time imaging of complementary information

The established applications of coregistered MRI and PET will gain new dimensions with the simultaneous procedures made possible by integrated PET/MR. Simultaneous data acquisition will allow the addition of kinetic, functional and metabolic information for real-time multiparametric imaging. The vascular origin of changes in cerebral blood flow, oxygen consumption and metabolism causing stroke and intracerebral and subarachnoid haemorrhages can be detected by MRA. Perfusion changes can be related directly to the extent of hypoxia (^{18}F-MISO-PET) and changes in metabolic markers (e.g. lactate, choline and N-acetyl-aspartate) can be assessed through simultaneous PW-MRI, MRS and ^{18}F-MISO-PET. Diffusion- and perfusion-weighted (DW-PW) MRI can be performed during PET measurements of ^{15}O and $H_2^{15}O$ for differentiation of intervascular perfusion, tissue blood flow, penumbra and irreversible tissue damage in ischaemic stroke [26]. This differentiation is important for therapeutic decision. For that purpose the validation of MR surrogate measures (mismatch between PW- and DW-MRI) is needed. The combination of various MRS procedures with PET will broaden the insight into the complex metabolic changes caused by brain diseases.

Coregistration of image data from the different modalities has indicated the value of such comparative studies in stroke [27], gliomas [28], and degenerative [29] and congenital or hereditary disorders [30]. However, coregistration was limited since it required multiple investigations in different laboratories. Real-time simultaneous studies will be of particular interest for the interpretation of activation patterns (intravascular versus tissue signals) obtained with fMRI and $H_2^{15}O$ (or FDG) PET [31, 32] and will be useful for the analysis of the effect of specific tasks on transmitter release and receptor binding, such as the determination of DOPA, raclopride and 5-hydroxytryptamine transporter by combining fMRI with PET [33–35]. A similar approach (fMRI and PET of receptor ligands) might be useful to elucidate the effects of drugs and their withdrawal (e.g. nicotine) on task performance. However, in these combined applications of fMRI and PET the differences in temporal resolution and sampling must be considered: separated short time frame MRI (~ seconds) versus PET acquisitions of several minutes.

Dynamic data for modelling

The high temporal resolution of MRI can be utilized for the acquisition of dynamic data can be utilized for the quantification of metabolic values by PET. For example, flow-dependent kinetic constants can be determined by PWI and used for compartmental analysis of PET data (e.g. FDG, FLT)
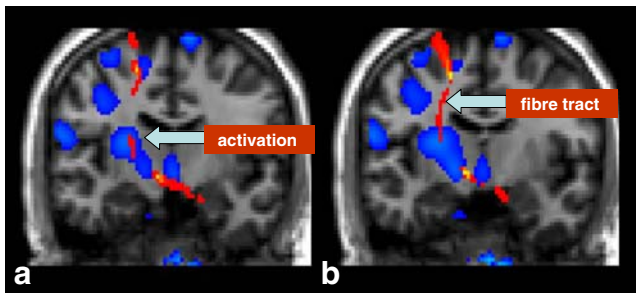
Fig. 4 Coregistration of MRI with diffusion tensor tracking and PET ^{15}O water activation studies demonstrates the effect of stimulation of the nucleus accumbens by flow increase in the striatum and various cortical regions. Diffusion tractography depicts the anatomical pathways between the stimulated region and the activated subcortical and cortical areas

[36] or for the assessment of the kinetics of the distribution of tracers or labelled drugs in various brain structures [37].

Simultaneous data acquisition by MRI and PET could also be used to develop new methods, e.g. values of cerebral blood flow obtained by arterial spin labelling MRI can be validated by H_2^{15}O-PET [38], and ^{17}O as a new MRI tracer for oxygen utilization [39] can be compared to cerebral metabolic rate of O_2 as determined by PET. This promising new MRI method uses inhalation of air enriched with ^{17}O$_2$ whereby the inhaled ^{17}O is converted into H_2^{17}O in proportion to the oxygen consumption. The metabolite H_2^{17}O perturbs the proton signal resulting in negative contrast on T2-weighted MRI. Thus, the signal intensity is proportional to oxygen consumption.
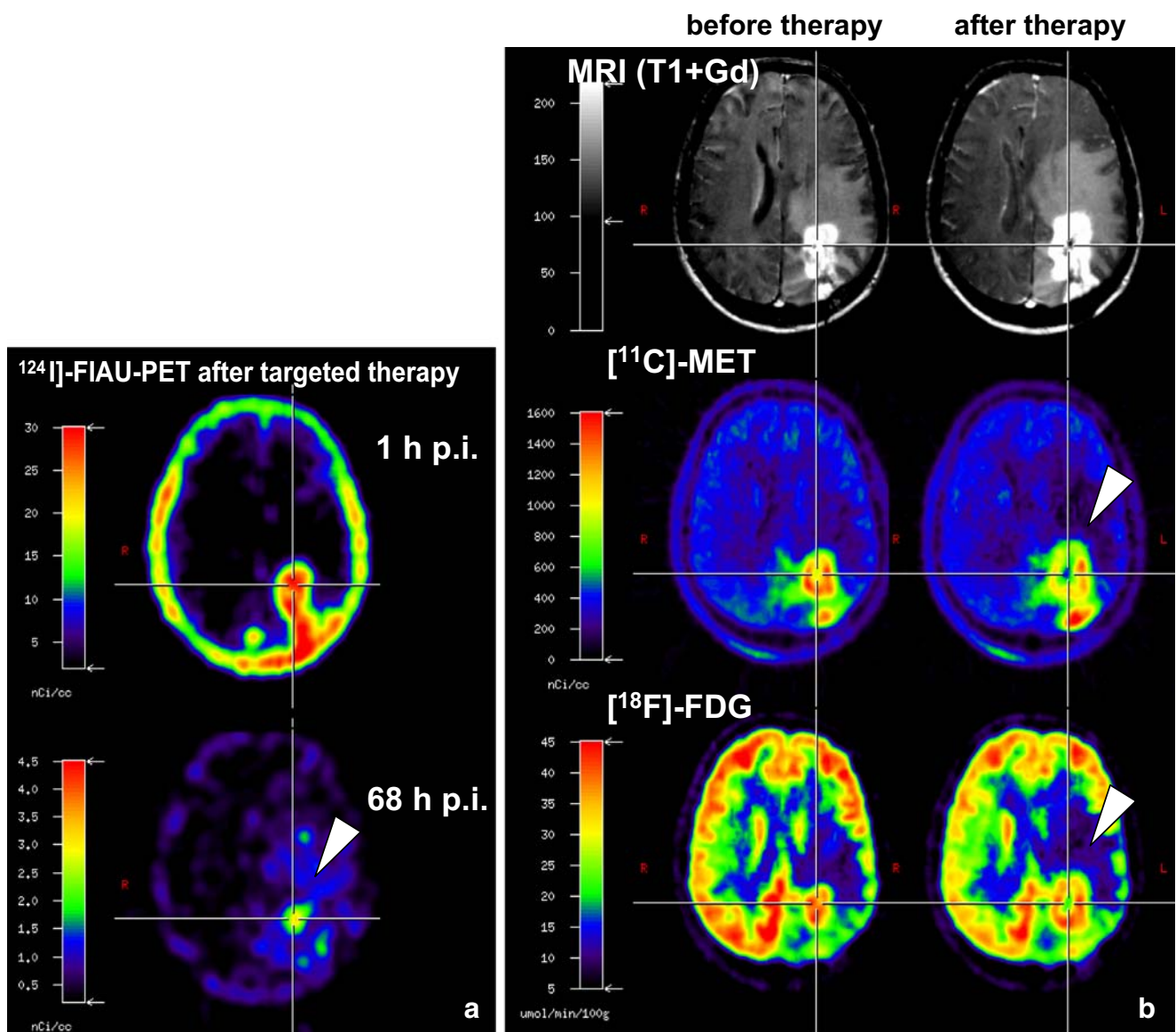

Fig. 5 Coregistration of FIAU-PET, MET-PET, FDG-PET and MRI for evaluation after targeted therapy in the active tumour centres, the effect of ganciclovir treatment is represented by the necrosis developing in the region of fialuridine accumulation. From Jacobs et al. [44]

Fig. 6 Images of stem cell migration toward the stroke territory by 3-D T2*-weighted MRI (**a**, **b**) and assessment of functional activity of implanted cells after migration to the stroke border zone (**c**, **d**). *Yellow arrows* indicate the implantation site (**a**), *red arrows* indicate migrating stem cells (**a**, **b**). Immunohistochemistry indicates differentiation of stem cells (green fluorescent protein) into neurons (neuronal specific nuclear protein) (**c**) and glial cells (glial fibrillary acidic protein) (**d**). From Hoehn et al. [47]
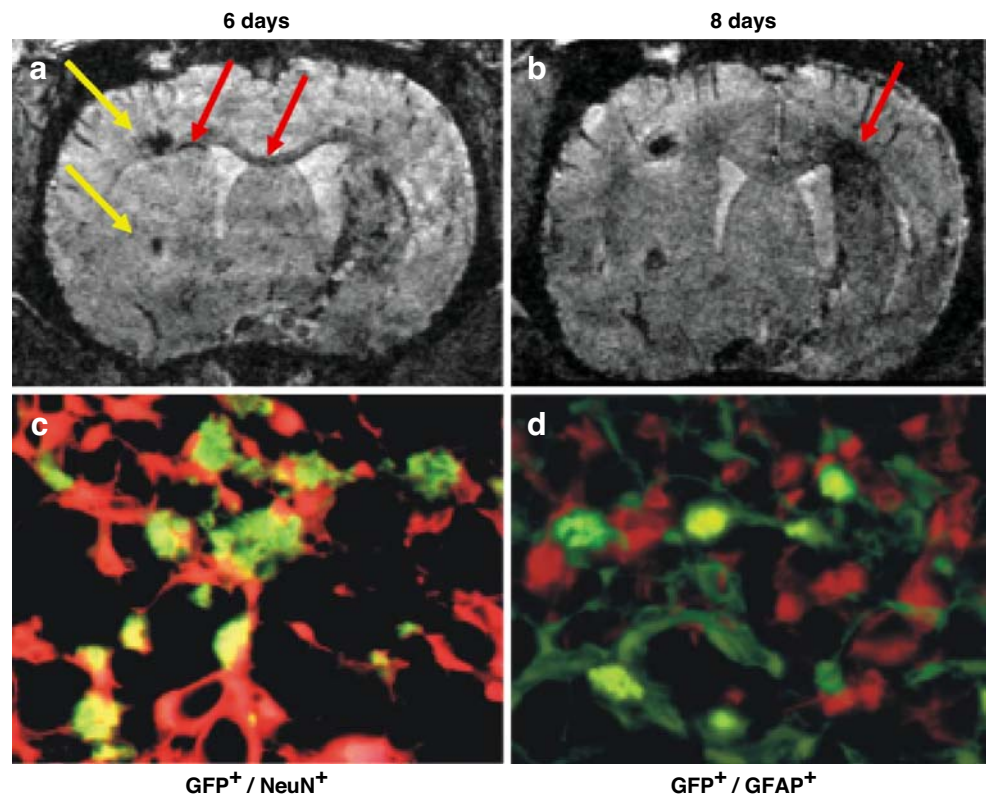
Multiparametric functional imaging

For complex studies of brain function special combinations of modalities or additional investigative procedures may open new insights into the organization of the brain and diseases–related changes of brain function. For these studies diffusion tensor tracking will add new dimensions, since it could be performed in close temporal relation to activation studies mapping the effects on transmitter release and receptor occupancy as well as on metabolism in connected areas of functional networks [40]. With this approach the effect of deep brain stimulation, which is a means to ameliorate neurological symptoms and to improve abnormal behaviour [41] could be demonstrated. The effect of such an invasive manipulation on metabolism in defined regions together with the connecting fibre tracts is shown in Fig. 4. It may also be possible to analyse the effect of repetitive transcranial magnetic stimulation (rTMS), which can be used to activate or inhibit selected areas of the cortex, on regional metabolism, and on the involvement of transmitter/receptor systems and the connecting network [42].

Perspectives for molecular and cellular imaging

Fusion of PET and MR images has been used in several attempts to identify molecular events induced by local pathogenetic factors, by the transfer of genetic material or implantation of (stem) cells. While the above studies were performed using separate imaging modalities, it is possible that these concepts could be transferred more easily to routine applications in humans through an integrated PET/MR tomograph, by which various functional and morphological aspects can be observed simultaneously. In several of these applications the identification of small regions or cell clusters by MRI might be essential for the analysis of biochemical processes by PET. Therefore, these examples may create new combined applications of MR and PET.

Angiogenesis is a fundamental process in various physiological and pathological processes. Visualization, quantification and monitoring of angiogenesis is of interest in various fields, including oncology and cardiology. Molecules regulating angiogenesis include growth factor receptors and integrins. Cyclic RGD peptides bind to integrin $\alpha_v\beta_3$, and ^{18}F-galacto-RGD has been tested in humans with high uptake in highly vascularized tumours. Alternatively, labelled ligands have been used to study the vascular endothelial growth factor receptor. When combined with dynamic, contrast-enhanced MR, yielding vascular and extravascular volumes, vascular permeability and perfusion angiogenesis PET markers may permit the follow-up of angiogenetic and antiangiogenetic treatment [43].

Targeted gene transfer by various vectors can be used to express foreign enzymes in cells. This strategy can be

applied to make malignant cells susceptible to specific drugs, which are toxic only to those cells expressing the enzymes. In an experimental glioma model the efficacy of this treatment strategy with transfer of the herpes virus thymidine kinase gene and application of ganciclovir has been demonstrated and preliminary clinical tests have shown some efficacy of this treatment [44]. The effect of this therapy can be followed by multitracer PET and verified on MRI (Fig. 5).

Implantation of embryonic stem cells into the striatum lesioned by injection of 6-OHDA in rats leads to proliferation and differentiation of dopaminergic cells. This was demonstrated by coregistering MRI and PET of the specific dopamine transporter ligands ^{11}C-CFT [^{11}C-2β-carbomethoxy-3β-(4-fluorophenyl) tropane] where CFT binding was restored in the region of TH-immunoreactive neurons documented post mortem. The restored functional activity of these implanted cells was demonstrated by the response to amphetamine, which caused an increase in rCBV due to dopamine release [45]. Simultaneous PET/MR can be used to show the viability and differentiation of transplanted cells and their effect on neuronal networks [46]

Cell replacement approaches are an innovative strategy for treatment of various neurological disorders. For the development of these approaches in animal models it is essential to monitor the location and to follow the migration of grafted stem or progenitor cells. Various strategies have been proposed for labelling these cells with ultrasmall superparamagnetic iron oxide particles and micron-sized iron oxide particles [47]. In focal experimental ischaemia labelled stem cells migrated over 3 weeks from the contralateral implantation site along the corpus callosum to the ventricular walls and massively populated the border zone of the damaged brain tissue on the lesioned hemisphere (Fig. 6). A combination of MRI for tracking cells and of PET for proving their biological activity could demonstrate the viability of the cells as well as their integration into functional networks [48]. Monitoring cell viability and migration by MRI combined with indicators of function from PET might also become a qualifying step in strategies relying on transplantation of fetal grafts, e.g. in Parkinson disease.

Conclusion

Integrated PET/MR holds great potential for brain research, especially for multiparametric analysis of complex function in neuronal networks, for the imaging of complex molecular processes of gene transfer and cell transplantation and for the translation of new treatment strategies from preclinical research into clinical application. If the superiority of integrated PET/MR in diagnostic accuracy and treatment monitoring can be proven and if the integration of the two modalities is cost effective it may also become an instrument for routine clinical use.

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