

# Simultaneous *in vivo* positron emission tomography and magnetic resonance imaging

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**Positron emission tomography (PET) and magnetic resonance imaging (MRI) are widely used *in vivo* imaging technologies with both clinical and biomedical research applications. The strengths of MRI include high-resolution, high-contrast morphologic imaging of soft tissues; the ability to image physiologic parameters such as diffusion and changes in oxygenation level resulting from neuronal stimulation; and the measurement of metabolites using chemical shift imaging. PET images the distribution of biologically targeted radiotracers with high sensitivity, but images generally lack anatomic context and are of lower spatial resolution. Integration of these technologies permits the acquisition of temporally correlated data showing the distribution of PET radiotracers and MRI contrast agents or MR-detectable metabolites, with registration to the underlying anatomy. An MRI-compatible PET scanner has been built for biomedical research applications that allows data from both modalities to be acquired simultaneously. Experiments demonstrate no effect of the MRI system on the spatial resolution of the PET system and <10% reduction in the fraction of radioactive decay events detected by the PET scanner inside the MRI. The signal-to-noise ratio and uniformity of the MR images, with the exception of one particular pulse sequence, were little affected by the presence of the PET scanner. *In vivo* simultaneous PET and MRI studies were performed in mice. Proof-of-principle *in vivo* MR spectroscopy and functional MRI experiments were also demonstrated with the combined scanner.**

molecular imaging | small animal imaging | multimodality imaging

**P**ositron emission tomography (PET) noninvasively images the distribution *in vivo* of biomolecules (small molecules, peptides, antibodies, and nanoparticles) labeled with radionuclides that undergo positron decay and produce back-to-back 511-keV annihilation photons (1). Because of the high sensitivity of radioactive assays, PET can measure picomolar concentrations of labeled biomolecules. A wide variety of molecular targets and pathways have been imaged by using PET radiotracers (2, 3), with the avid accumulation of the radiotracer [<sup>18</sup>F]-2-fluoro-2-deoxy-D-glucose (FDG) in malignant tumors being just one example that has widespread applications in the clinic and in the study of therapeutic strategies for tumor treatment in animal models. However, the spatial resolution of PET is limited by physical factors associated with positron physics and by the difficulty of acquiring sufficient counting statistics. Furthermore, PET images often lack definitive anatomic information, making interpretation of the precise location of radiotracer accumulation difficult.

Magnetic resonance imaging (MRI) can provide high-spatial-resolution anatomic images with exquisite soft-tissue contrast by exploiting the differences in relaxation times of protons in different biochemical environments (4, 5). The combination of high spatial resolution and contrast allows the anatomic consequences (e.g., tumor growth, brain atrophy, cardiac wall motion abnormalities) of many disease processes to be visualized in patients and in animal models. Functional MRI techniques can

measure important physiologic parameters, including diffusion (6, 7), permeability (8), and changes in blood oxygenation levels after neuronal activation (9–11). The addition of passive contrast agents based on gadolinium or iron-oxide nanoparticles can further enhance contrast (12). A number of laboratories are also developing targeted MRI contrast agents (13–15). MR spectroscopy (MRS), which measures the shift in the frequency at which protons in different chemical environments resonate, allows the relative concentrations of abundant metabolites, and some drugs administered at mass levels, to be measured. With localized MRS, coarse spectroscopic images also can be obtained (16, 17). Proton MRS is particularly useful in tumor studies and also offers information about neuronal integrity in neurodegenerative disorders (18–21). However, the molar sensitivity of MRI for different metabolites and tracers is many orders of magnitude lower than that of PET, imposing significant restrictions on the kinds of targets that can be visualized.

Clear synergies exist between the two modalities, because each can provide unique information not attainable with the other modality. For this reason, MRI and PET are frequently combined in clinical diagnostics and research. Relevant to this work, these modalities have been increasingly used in more basic biomedical research, particularly in efforts to understand the etiology and evolution of human diseases in appropriate animal models (commonly mice and rats) and in the preclinical evaluation of new therapeutic strategies, including small-molecule drugs, peptides and antibodies, cellular therapies, gene therapy, and nanoparticle-based therapies. In particular, these modalities can be used in combination to study both the pharmacokinetics and pharmacodynamics of new therapeutics.

To date, PET and MR images are acquired on separate imaging systems and typically coregistered by using software that makes use of the information content of the image data (e.g., landmarks) or external fiducial markers that can be clearly identified in the two images (22). This approach works well in the brain, where the skull constrains movement and enables simple rigid body registration methods to be used (23). However, it becomes more problematic in the thorax, abdomen, and pelvic regions, where tissues and organs deform based on the position of the subject in the scanner, and where temporal changes such as emptying of stomach contents, movement of the food through

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the intestinal tract, and filling of the urinary bladder also confound registration. Deformable image registration techniques can be used, but their success is highly situation-dependent, and they are not generally robust in the presence of significant tissue movement between the two separate imaging studies. Simultaneous acquisition, therefore, would guarantee spatial registration of the two datasets.

More crucially, sequential PET and MRI scanning does not permit temporal correlation of PET and MRI studies. Biological systems are inherently dynamic, and their response to drugs and contrast agents is strongly time-dependent. The biodistribution of most contrast agents and drugs exhibits changes on time scales of seconds to minutes. To ensure that a subject is being imaged in the same physiologic state, and to correlate changes over time in the PET and MRI signals in response to an intervention, thus often requires that the data be acquired simultaneously. To give just one example, one might want to monitor dynamic changes in tumor physiology with MRI [e.g., cellularity by diffusion measurements (24), macromolecular environment (25, 26), vasculature by contrast enhancement (27)] while imaging the delivery of a radiolabeled therapeutic agent to, or assessing the biochemistry of, the tumor. Simultaneous acquisition of PET and MRI data by using an integrated imaging device is, therefore, necessary to answer many important biomedical questions in dynamic, living systems.

In designing an integrated scanner for simultaneous PET and MR imaging, an obvious challenge relates to the ways in which the PET and MRI systems can interfere with each other, leading to major artifacts and/or image degradation. The primary concerns are electromagnetic interference (EMI) and the effect of the main magnetic field ( $B_0$ ) of the MRI on the detectors in the PET scanner; however, other, more subtle, effects that need to be considered include the induction of eddy currents, susceptibility artifacts, and an increase in temperature or vibrations induced by the running of MR sequences. The detectors [usually based on scintillators coupled to photomultiplier tubes (PMTs)] and associated electronics commonly used in PET scanners are sensitive to magnetic fields and contain conducting and radio-frequency (RF) radiating components that have the potential to interfere with the MRI system. For instance, PMTs are affected by even weak magnetic fields. The PET electronics can also easily pick up the strong RF signals generated by the RF coil in the MRI. Furthermore, the  $B_0$  homogeneity in MRI must not be significantly degraded by the introduction of diamagnetic or paramagnetic materials and, where possible, any materials introduced into the magnet should be arranged symmetrically to minimize possible artifacts. Because of their high susceptibility, ferromagnetic materials are not normally useful, or even tolerable, within the magnetic field of the MRI and consequently are to be avoided.

The very earliest approaches to developing MRI-compatible PET systems used very long optical fiber connections between the scintillator elements and the PMT to effectively eliminate EMI between the two systems (28, 29). Although this led to proof-of-principle data, including a small number of animal studies, the performance of the PET scanner was poor compared with stand-alone PET scanners, and the length of the optical fibers made the system cumbersome. A variation on this design (30), using a split magnet in which the PET detectors reside in the gap and the fibers emanate radially from the magnet, offers the prospect of improved PET performance, albeit still limited by the transmission of scintillation light through very long optical fibers and the low field strength of the magnet compared with most preclinical MRI scanners.

We opt for a different approach in developing a PET scanner insert that is compatible with existing high-field animal MRI systems. We use magnetic field-insensitive avalanche photodiode (APD) detectors in place of PMTs and use very short optical

fiber bundles to appropriately position the photodetectors and PET electronics with respect to the MRI RF and gradient coils, to minimize interference. A detailed description of the construction of the MRI-compatible PET insert was published in ref. 31. In brief, the PET insert comprises 16 detector modules arranged in a symmetric ring. Each PET detector module consists of an array of lutetium oxyorthosilicate (LSO) detectors coupled through a bundle of bent optical fibers to a position-sensitive APD (PSAPD) and charge-sensitive preamplifiers mounted on a printed circuit board populated with nonmagnetic components. All 16 modules are mounted on a carbon fiber tube, and the crystals in the LSO arrays form eight complete detector rings at the center of the insert [see [supporting information \(SI\) Fig. 5A](#)]. The PSAPDs and photodetectors are shielded by a copper laminate and are located in the MRI scanner such that they are axially outside of the linear region of the z-gradient field and outside of the imaging volume defined by the RF coil ([SI Fig. 5B](#)). The detectors are cooled to  $-10^\circ\text{C}$  using chilled dry air to obtain optimal signal-to-noise from the PSAPDs and to minimize temperature drift. Details of the PET insert geometry are provided in [SI Table 1](#). The PET insert is compatible with existing preclinical MRI scanners having a clear bore of 12 cm or greater ([SI Fig. 5C](#)). The PET insert is positioned in the MRI scanner by using a registration scan with PET- and MRI-visible fiducial markers such that the isocenters of the PET and MRI fields of view (FOVs) are coincident. The PET insert is readily removed, allowing it and the MRI scanner to be used as independent devices.

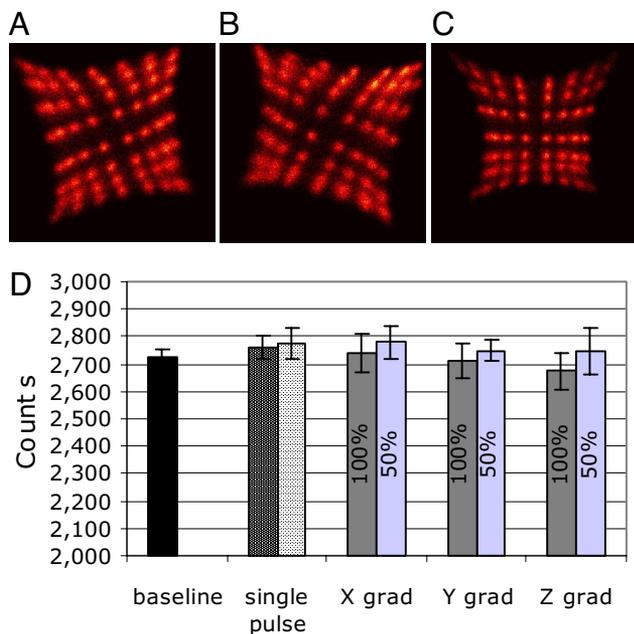
Other groups have pursued similar approaches but without the optical-fiber connection, placing the APDs and electronics in the active MR imaging volume (32, 33). This approach will improve PET performance by eliminating scintillation light loss in the optical fibers; however, the proximity of the APDs to the RF coil and gradients have the potential to increase interference between the systems, especially for MRI pulse sequences that demand intensive gradient-switching and high-intensity RF pulses.

Here we describe detailed phantom experiments performed with our MRI-compatible PET instrument to demonstrate that PET and MR images can be acquired simultaneously without significant interference between the two modalities. We also carried out a number of proof-of-principle *in vivo* studies to highlight the biomedical applications for this technology.

## Results and Discussion

**MRI System Effects on PET Imaging.** Experiments to examine the interference between the two imaging systems when acquiring PET and MR data simultaneously were designed to characterize the effect of one system's image acquisition protocol on the other. PET detector maps (which show a histogram of the events detected by the  $8 \times 8$  scintillator elements in a particular PET detector module when it is uniformly irradiated with a source of 511-keV annihilation photons) demonstrate a small rotation (clockwise or anticlockwise, depending on the orientation of the PSAPD with respect to the magnetic field) when the PET insert is inside the magnet (Fig. 1 *A* and *B*), due to the magnetic force on electrons moving through the silicon. However, the ability to resolve the detector crystals, which is a key factor contributing to the spatial resolution in PET, was not appreciably altered in the 7-T magnet.

Acquiring an MR image requires the use of strong RF pulses and rapidly switched magnetic field gradients that have the potential to perturb the weak electronic signals produced by the PET detectors. Therefore, PET measurements were taken while running MRI sequences that are normally used in small-animal studies, such as RARE (rapid acquisition with relaxation enhancement) and FLASH (fast low-angle shot). RARE is a fast spin echo (SE) sequence in which a number of  $180^\circ$  rephasing

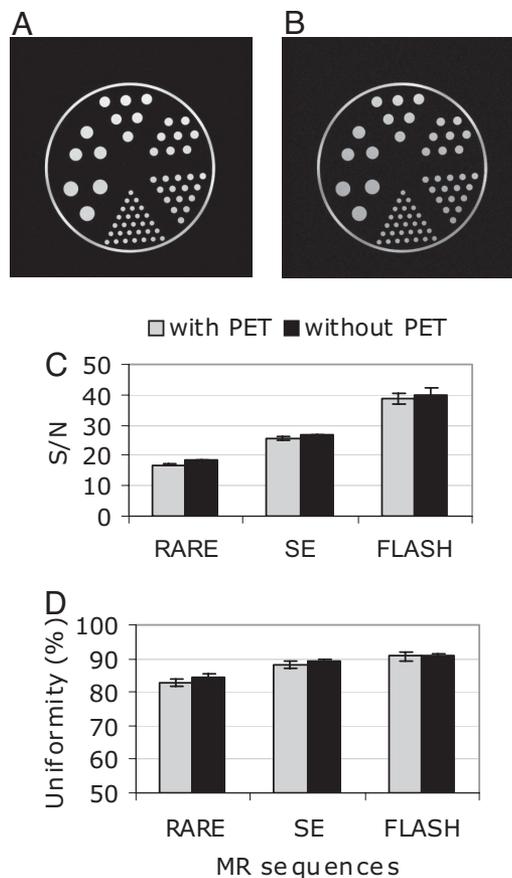


**Fig. 1.** MR scanner effect on PET system. (A–C) Detector histograms showing the anticlockwise (A) and clockwise (B) rotations of the crystal maps when compared with the data acquired outside of the magnet (C). (D) PET event rate measured under different conditions: (i) while applying only RF power (with 1,000 ms and 500 ms repetition times) and (ii) while switching the x–z gradients independently (at 100% and 50% power; 400 and 200 mT/m, respectively). Baseline represents the event rate recorded without running MR sequences.

pulses are applied after each 90° excitation pulse to create an echo train. FLASH is based on a gradient echo (GE) sequence in which a low flip angle and a very fast repetition rate are used.

No difference in spatial resolution [expressed in terms of full-width-in-half-maximum (FWHM)] of the PET scanner could be observed when operated in the MRI scanner with RARE (1.18 ± 0.02 mm), SE (1.19 ± 0.01 mm), or FLASH (1.19 ± 0.01 mm) pulse sequences versus the spatial resolutions of 1.19 ± 0.01 mm measured within the magnet without running pulse sequences. This demonstrates that there is no observable spatial distortion of the PET data in the MRI environment. The energy resolution of the PET detectors (which is important for rejecting annihilation photons that have inelastically scattered in the body and lost their positional information) is also unchanged during MRI pulse sequences (SI Table 2). The measured absolute sensitivity (fraction of radioactive decays leading to a detected event in the PET scanner) of the PET insert was 0.6% at the center of the FOV (CFOV). No change in sensitivity was detected while running a standard SE sequence. However, a 10% and 7% decrease in event rate was observed while running the FLASH and RARE sequences, respectively. This suggests that a small fraction of events are removed from the PET data stream. Further experiments in which RF excitation and gradient switching were applied separately revealed that the effect is likely caused by the gradient switching (Fig. 1D). This interference only occurs over a small fraction of the duty cycle of the pulse sequence, and these events are rejected by the PET scanner because they do not meet the pulse-height criteria.

**PET System Effects on MR Imaging.** The presence of the PET insert in the magnet has the potential to cause artifacts or to degrade the signal-to-noise ratio (SNR) in the MR signal, both of which would reduce image quality. Therefore, MR images were compared with and without the PET insert. MR images of a



**Fig. 2.** PET insert effects on MR imaging. (A and B) SE (A) and GE (B) images of a structured phantom acquired in the presence of the PET insert. (C and D) SNR (C) and uniformity (D) measured for several pulse sequences with and without the PET insert, using a uniform phantom.

structured phantom acquired in the presence of the powered PET insert with standard pulse sequences show no distortion and no obvious artifacts (Fig. 2A and B). Subtracted images, in the presence of the powered and unpowered PET insert, demonstrate a featureless noise background (SI Fig. 6). In a separate experiment, average SNR (Fig. 2C) and image uniformity (Fig. 2D) were measured with and without the PET insert for different pulse sequences, using a homogeneous phantom. The largest decrease in SNR caused by the PET insert was with the RARE sequence (–8%,  $P = 0.0001$ ), whereas a smaller decrease (–3%,  $P = 0.0001$ ) was observed for the SE sequence. Similarly, the largest decrease in uniformity was noted for the RARE sequence (–2%). Smaller changes (–1%) were observed for the SE sequence and no changes were noted for the FLASH sequence.

**In Vivo Small-Animal Simultaneous PET and MR Imaging.** *In vivo* mouse imaging studies revealed that the combined multimodality system produces consistent information in a real-world setting. A mouse injected with 10<sup>6</sup> MC38 cells was imaged after 10 days, when the tumor had reached ≈9 mm in diameter. Simultaneous imaging with FDG PET and anatomic MRI (Fig. 3A) shows a hyperintense focus of FDG uptake coincident with the tumor site. Uptake is heterogeneous, and a region of hyperintensity on MRI close to the center of the tumor shows low FDG uptake (see arrow in Fig. 3A), likely indicative of necrosis. This example shows the potential for combined PET/MRI studies to improve the interpretation of cancer imaging studies in heterogeneous tumors containing malignant tissue,





**In vivo MR spectroscopy.** Volume-selective *in vivo*  $^1\text{H}$  spectroscopy was performed in the presence of the powered PET insert, with a cubic voxel of  $3 \times 3 \times 3$  mm<sup>3</sup> positioned centrally in the mouse brain. A point-resolved spectroscopy (PRESS) sequence with TR/TE = 2,500/12 ms was used. Water suppression was achieved by using a VAPOR module. The total acquisition time was 30 min.

**EPI.** A four-shot EPI sequence with linear ramp (ramp time = 220  $\mu\text{s}$ ) was used with a 25-mm head-only RF coil with TR/TE = 2,000/32 ms, bandwidth = 250 kHz, and 16 averages, for a total acquisition time of  $\approx 10$  min. Five slices were acquired with FOV =  $1.92 \times 1.92$  cm, matrix size =  $128 \times 128$ , slice thickness = 0.75 mm. For diffusion weighting:  $\Delta = 14$  ms;  $\delta = 7$  ms; five  $b$  values were used (100, 200, 600, 800, and  $1,400 \times 10^{-3}$  sec/mm<sup>2</sup>) along the dorsoventral direction. ADC maps were calculated in the standard manner (36).

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