Title: The Integration of Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) Will Transform Medical Imaging

Authors: *Frank S.Prato[1,2,3*], R. Terry Thompson[1,2,3], John Butler[1], William Pavlosky[1,2]*

Affiliations:

[1]Imaging Program, Lawson Health Research Institute
268 Grosvenor Street, B5-004, London, ON, Canada, N6A 4V2
prato@lawsonimaging.ca, thompson@lawsonimagng.ca, jbutler@lawsonimaging.ca,
William.Pavlosky@lawsonimaging.ca

[2]Diagnostic Imaging, St. Joseph's Health Care, London, ON
268 Grosvenor Street, London, ON, Canada, N6A 4V2

[3]Dept. of Medical Biophysics, University of Western Ontario, London, ON
Medical Sciences Building Room M407 London, Ontario, Canada, N6A 5C1

Abstract

Hybrid imaging has been a growing area in medical imaging. This has been driven by: a) the complimentary information provided by different technologies and b) the growing awareness that functional, metabolic and molecular events often occur in times too short to be captured by sequential imaging by different modalities. To address these needs Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) have been integrated into one platform. To achieve this PET technology had to be significantly modified and MR technology appropriately adapted. The technical challenges that have been met and the future benefits anticipated will be presented.

1.Introduction

Initially the first approach to combine complimentary information from different imaging technologies was to use software to register (i.e. fuse) in three dimensions images acquired at different times. However this puts severe limitations on the need for similarity in spatial image information between the different imaging modalities. This was then addressed by acquiring images sequentially from different modalities wherein registration (fusion) was achieved by hardware implementation rather than software. For example on a PET/CT imaging system first the PET image is acquired and then the table with the patient is moved and then the X-ray CT image is acquired. Provided the patient does not move relative to the table then images of body parts that have not moved between the PET and X-ray CT acquisitions are registered directly. However, body parts that move due to physiological motion such as breathing may not be properly superimposed. This allows registration of PET and CT images without the limitations imposed by software registration but has not addressed the need of simultaneity to a) allow correction of movement due to physiological processes and b) capture complementary information at the same time. To address both registration and simultaneity needs a number of research laboratories and two major medical imaging equipment manufacturers have incorporated magnetic resonance imaging (MRI) with positron emission tomography (PET) into a hybrid platform capable of true simultaneous data acquisition over the same imaging volume [1].

The bringing together of Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) into one hybrid platform capable of simultaneous data acquisition over the same imaging volume has been on the one hand, technically challenging and, on the other hand, of considerable future anticipated value.

PET will, over the next 10 to 20 years, be the modality to drive molecular imaging in personalized medicine. In the past PET provided quantitative functional imaging (e.g. brain and heart blood flow) and metabolism (e.g. detection of cancer spread by up regulation of glycolisis in metastatic disease). In the near future its role will be to lead molecular imaging needed to understand and diagnose diseases such as mental health disorders (e.g. schizophrenia, affective disorders), other neurological disorders (e.g. Parkinson's, dementias), differentiation of cancer subtype (e.g. breast and prostate disease) and early detection of cardiovascular disease. PET will lead human molecular imaging because a) it has the greatest sensitivity of any non-invasive medical imaging modality (can detect picomolar concentrations of a PET probe to a disease specific biomarker) and b) it is the only non-invasive medical imaging modality with a proven track record of getting new imaging probes into human use. However PET has one major limitation; it can only identify one signal common to all PET radionuclides and hence can only detect one PET probe at a time i.e. is effectively uni-spectral.

MRI is an ideal partner to PET because a) it provides anatomical information equivalent to that of x-ray CT without exposure to ionizing radiation, b) it has the greatest soft tissue contrast of any anatomical imaging modality and c) it can provide complimentary information such as blood flow, water diffusion, brain fiber tracks, odema etc. as MRI is effectively

978-1-4673-5225-3/14/$31.00 ©2014 IEEE

multi-spectral. In addition it has recently been shown that electroencephalography (EEG) and electromyography (EMG) can be acquired simultaneously with MRI allowing MR/PET to expand to MR/PET/EEG/EMG hybridization.

2. Technical Challenges

Simultaneous acquisition of PET and MRI data over the same imaging volume is possible because both of these modalities use volume acquisition strategies without the need of moving detectors. However it was technically difficult to achieve a hybrid configuration which did not compromise result in performance of the PET and MRI components compared to stand-alone PET and stand-alone MR platforms.

The major adaptation that had to be achieved for the PET part of the MRI/PET platform was the replacement of the magnetic field sensitive photo multiplier tube [2]. This has initially been achieved with avalanche photo-diode (APD) technology [2]. More recently Geiger-mode APDs (i.e. silicon photo multipliers which will also operate in strong magnetic fields) have been developed that have better timing resolution, are less sensitive to temperature variations, require lower bias voltages and have higher gain than the APD [3,4].

The major adaptation for the MRI part of the MR/PET platform was to determine how the MRI data could be used to direct attenuation and scatter correction of the 511 keV annihilation photons which must be detected in PET. Correction for the attenuation and scatter of the 511 keV photon is essential otherwise images are badly distorted and quantitation not possible. The problem is that MRI data is dependent on proton density and nuclear magnetic resonance (NMR) relaxation rather than the needed quantity of electron density. As well NMR relaxation is so fast in cortical bone and lung that conventional MRI retrieves no signal from these two tissues which have the greatest (bone) and smallest (lung) electron densities. Currently this challenge is being addressed by segmenting out different tissues from the MRI and assigning to them 511 keV attenuation coefficients [5]. However these average coefficients vary between subjects and there is a need to use patient specific coefficients to improve quantitation [6]. More recently a new MRI approach using Ultrashort TE (UTE) technology may resolve this impasse by allowing the needed signal to be retrieved from bone and lung [8]. In addition, to further reduce the extent of attenuation and scatter of the 511 keV photons, the radiofrequency coils that need to be placed between the patient and the 511 keV detectors were redesigned to reduce attenuation [1]. Finally this was all brought together in a commercial product by Siemens Healthcare in 2011 (see Figure 1).

3. Anticipated Benefits

It is anticipated that simultaneous PET with MRI will greatly add to our knowledge of brain diseases [9] and cardiovascular disease [10] while improving our ability to diagnose cancer and follow its treatment [11]. Some specific examples:

a) Each coincident detection of 511 keV photons will be corrected for subject motion which will improve PET spatial resolution (has already been demonstrated in the brain [8]).
b) PET data will be synchronized to physiological motion including cardiac and respiratory [12].
c) PET images of metabolism will be matched to brain blood flow images. This will be the first time that metabolism by PET can be simultaneously linked to blood flow which will be particularly important in understanding the pathophysiology of dementias [13].
d) In schizophrenics the dopaminergic neurotransmitter pathway (by PET) will be compared simultaneously, for the first time, to the glutamatergic neurotransmitter pathway (by MRI). MRS (P-31 and H-1) could be added to the examination to further elucidate the ongoing biochemistry [14,15].
e) In pain opioid receptor occupancy (by PET) will be compared to neuronal activation in the pain matrix (by MRI) [16,17,18].
f) In Alzheimer disease the plaque burden (by PET) will be compared to micro vascular disease as measured by quantitative blood flow (by MRI) [13].
g) In Parkinson's disease the impact of transplanted adult progenitor cells (by PET) will be compared to their location (by MRI) [19].
h) In cardiology we will be able to precisely determine the evolution in time of inflammation and how it leads to heart failure [16].
i) In cancer of the breast and cancer of the prostate we will be able to identify sub-disease type and hence treat each patient with the optimal treatment [20,21].

Of course many more examples come to mind. The exciting part is that this is just the beginning as new PET molecular probes are being developed monthly and MRI techniques continue to evolve. For example a hybrid platform in which EEG is added to PET/MRI would allow the determination of how neuronal events on the time scale of a 100 ms (EEG) are related to minute by minute changes in blood flow changes (MRI) and changes in receptor activation/occupancy integrated over 10s of minutes (PET) [9]. Hybrid PET/MRI will transform medical imaging which we can predict based on what we already know separately about PET and MRI. But it will cause much greater transformation in our understanding of

disease based on what we will discover as this new tool will give us new insight that we cannot foresee. As Yogi Berra said, "The future ain't what it used to be" [22].

4. Figures

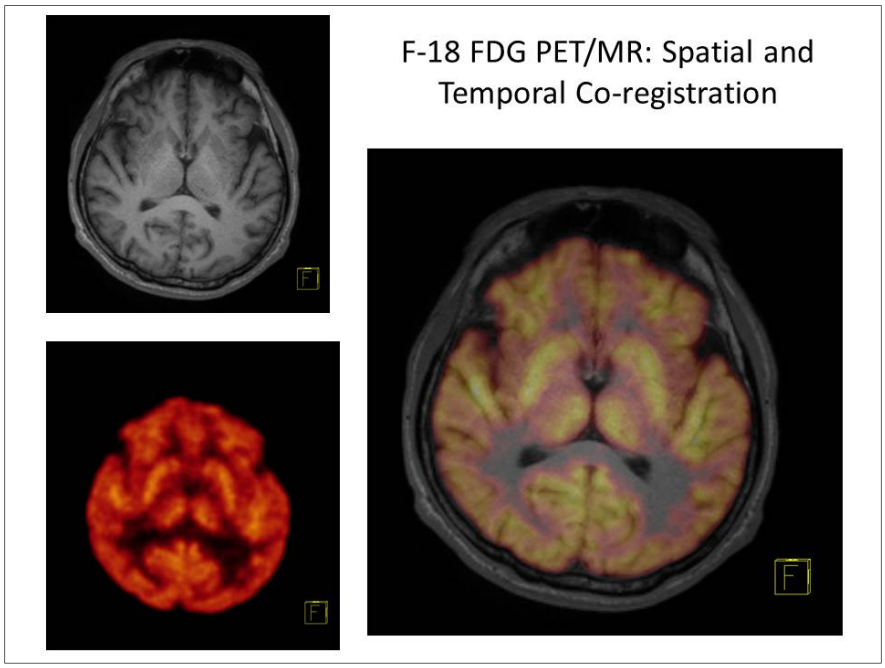

Figure 1 – A brain MRI anatomical image (upper left) and a PET glucose metabolism image (lower left) are de facto superimposed in three dimensional space (right image) as the MRI and the PET image were acquired at the same time over the same imaging volume using a hybrid PET/MRI medical imaging system (Biograph mMR, Siemens Healthcare)

5. References

[1] Delso G, Fürst S, Jakoby B, Ladebeck R, Ganter C, Nekolla SG, Schwaiger M, Ziegler SI. Performance measurements of the Siemens mMR integrated whole-body PET/MR scanner. *J Nucl Med*. 2011 Dec;52(12):1914-22

[2] Pichler B, Lorenz E, Mirzoyan R, Pimpl W, Roder F, Schwaiger M, Ziegler SI. Performance test of a LSO-APD PET module in a 9.4 Tesla magnet. *Nuclear Science Symposium. 1997 IEEE,* 1997, 2, 1237-1239

[3] Klausen LT, Keller HS, Olesen VO, Aznar M, Andersen FL. Innovations in PET/CT. *Q J Nucl Med Mol Imaging*, 2012 Jun;56930:268-79

[4] Roncali E, Cherry SR. Application of Silicon Photomultipliers to Positron Emission Tomography. *Ann Biomed Eng,* 2011 April; 39(4);1358-1377

[5] Marshall HR, Stodilka RZ, Lewden B, Théberge J, Sabondjian E, Legros AG, Mitchell AJ, Deans L, Sykes JM, Thompson RT, Prato FS. MR-based whole-body PET attenuation correction in hybrid PET/MRI: A computationally inexpensive algorithm for T1, T2 and proton density weighted images. *Proceedings of the 18th scientific meeting & exhibition of the International Society of Magnetic Resonance in Medicine (ISMRM),* May 1 – 7, 2010, Stockholm, Sweden

[6] Heiss WD. The potential of PET/MR for brain imaging. *Eur. J. Nucl. Med. Mol. Imaging*, 2009, 36, S105 –S112

[7] MessiouC, Collins DJ, Morgan VA, Robson MD, deBono JS, Bydder GM, deSouza NM. Quantifiying sclerotic bone metastases with 2D ultra short TE MRI: a feasibility study. *Cancer Biomark,* 2010;7(4);211-8

[8] Catana C, Drzezga A, Heiss WD, Rosen BR. PET/MRI for neurologic applications. J Nucl Med, 2012 Dec;53(12):1616-25

[9] Shah NJ, Oros-Peusquens AM, Arrubla J, Zhang K, Warbrick T, Mauler J, Vahediopour K, Romanzetti S, Felder J, Celik A, Rota-Kops E, Iida H, Langen KJ, Herzon H, Neuner I. Advances in multimodal neuroimaging: hybrid MR-PET and MR-PET-EEG at 3T and 9.4T. *J Magn Reson.*. 2013 Apr;229:101-15

[10] Rischpler C, Nekolla SG, Dregely I, Schwaiger M. Hybrid PET/MR imaging of the heart: potential, initial experiences and future prospects. *J Nucl Med.* 2013 Mar;54(3):402-15

[11] Balyasnikova S, Lofgren J, de Nijs R, Zamogilnaya Y, Hojgaard L, Fischer BM. PET/MR in oncology: an introduction with focus on MR and future perspectives for hybrid imaging. *Am J Nucl Med Mol Imaging,* 2012;2(4):458-74
[12] White JA, Rajchl M, Butler J, Thompson RT, Prato FS, Wisenberg G. Active Cardiac Sarcoidosis: First Clinical Experience of Simultaneous PET/MRI Imaging for Diagnosis of Cardiac Disease. Circulation 2013 June 4;127(22):e639-41
[13] Anazodo U, Stodilka RZ, Butler J, Mandel J, Thompson RT, Prato FS, Wang DH, St. Lawrence K. Simultaneaous imaging of cerebral perfusion and glucose metabolism by PET/MRI. *ISMRM 21st Annual Meeting and Exhibition,* Salt Lake City, Utah, USA. April 20 – 26, 2013
[14] Stanley JA, Williamson PC, Drost DJ, Carr T, Rylett RJ, Malla A, Thompson RT: An in Vivo Study of the Prefrontal Cortex of Schizophrenic Patients at Different Stages of Illness via Phosphorus Magnetic Resonance Spectroscopy. Archives of General Psychiatry 52:399-406, 1995
[15] Stanley JA, Williamson PC, Drost DJ, Rylett RJ, Carr T, Malla A, Thompson RT: An in Vivo Proton Magnetic Resonance Spectroscopy Study of Schizophrenia Patients. Schizophrenia Bulletin 22(4):597-609, 1996.
[16] Owen DG, Bureau Y, Thomas AW, Prato FS, St. Lawrence K. 2007. Quantification of pain-induced changes in cerebral blood flow by perfusion MRI. Pain. 2008 May:136(1-2): 85-96
[17] Ravert HT, Bencherif B, Madar I, Frost JJ. 2004. PET imaging of opioid receptors in pain: progress and new directions. Curr Pharm Des. 2004:10(7):759-768
[18] Robertson JA, Thomas AW, Modolo J, Miller J, Juen N, Legros A, Prato FS. Evolution of hybrid functional imaging in bioelectromagnetics research. *Environmentalist*, 2011
[19] Goldhawk DE, Rohani R, Sengupta A, Gelman N, Prato FS. Using the magnetosome to model effective gene-based contrast for magnetic resonance imaging. *Nanomed Nanobiotechnol*. 2012 Jul-Aug;4(4):378-88
[20] Pace L, Nicolai E, Luongo A, Aiello M, Catalano OA, Soricelli A, Salvatore M. Comparison of whole-body PET/CT and PET/MRI in breast cancer patients: Lesion detection and quantification of 18F-deoxyglucose uptake in lesions and normal organ tissues. *Eur J Radiol.* 2014 Feb;83(2):289-96
[21] Afshar-Oromieh A, Haberkorn U, Schlemmer HP, Fenchel M, Eder M, Eisenhut M, Hadaschik BA, Kopp-Schneider A, Rothke M. Comparison of PET/CT and PET/MRI hybrid systems using a 68Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience. *Eur J Nucl Med Mol Imaging,* 2013 Dec 19, [epub ahead of print]
[22] Berra Y (http://www.yogiberra.com/yogi-isms.html)

6. Acknowledgements

This research was funded in part with grants from, the Canadian Foundation for Innovation, the Canadian Institutes of Health Research and the Ontario Research fund. Further financial support was provided by St. Joseph's Health Care, Multi-Magnetics Incorporated, Siemens Canada and London X-Ray Associates. The authors would also like to thank Dr. Gerald Moran of Siemens Canada and Dr. Jonathan Thiessen for technical assistance and Ms. Shelagh Ross for manuscript preparation.