PET – MR: Opportunities in the Clinical Setting & Beyond


NIH (NIBIB, NCI, NHLBI, NIMH, NINDS, NIDCD, OD) HHMI
Outline

• Improving Lesion Detection Accuracy in Oncologic PET – MR
• Exploring Cardiac Structure & Function with PET – MR
• Neurology and Neuroscience
• Imaging Guidance & Monitoring in Radiation Therapy Planning
Outline

• Improving Lesion Detection Accuracy in Oncologic PET – MR
• Exploring Cardiac Structure & Function with PET – MR
• Neurology and Neuroscience
• Imaging Guidance & Monitoring in Radiation Therapy Planning
<table>
<thead>
<tr>
<th><strong>PET</strong></th>
<th><strong>MR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>High sensitivity</td>
<td>Exquisite high resolution, excellent soft tissue contrast</td>
</tr>
<tr>
<td>Absolute quantitation</td>
<td>Non ionizing</td>
</tr>
<tr>
<td>Good Time resolution</td>
<td>Excellent time resolution</td>
</tr>
<tr>
<td>Poor spatial resolution</td>
<td>Poor sensitivity</td>
</tr>
<tr>
<td>Limited anatomic information</td>
<td>Absolute quantitation challenging</td>
</tr>
</tbody>
</table>
Integrated Whole-Body MR-PET @ MGH

Simultaneous PET – MR (mMR)

25 cm axial coverage

60 cm
Clinical value of PET-MR in detecting small liver lesions

66 year-old woman with inflammatory bowel disease and an incidentally-discovered liver lesion. Axial T2 and axial postcontrast (Eovist) images demonstrate an indeterminate suspicious dominant hepatic lesion (Fig 2a-b). Lesion was biopsied and found to be cholangiocarcinoma, and was FDG-avid on PET-CT staging exam (Fig 2c). Many smaller lesions were also seen on MR (Fig 2d), but were not confidently identified on PET or CT (Fig 2e-f).
Clinical Value of PET-MR in OB-GYN

OB-GYN Metastatic Staging

45 y.o. F, melanoma of right thigh. Ovary in ovulatory phase or lymph node metastasis?

G. El Fakhri, Ph.D.
Clinical Applications of PET-MR in Pediatrics

Neuroblastoma

Whole-Body STIR MRI and $^{18}$F-FDG PET Extensive bone marrow metastasis on PET

G. El Fakhri, Ph.D.
Rationale: Motion deteriorates PET image quality

- Blurring
- Lower Noise

Uncorrected

- Using all PET data at all motion phases without motion correction

Gated

- Freezing Motion
- Higher Noise

- Using some PET data only at one motion phase

Solution 1: Using all PET data with MR-based motion correction

G. El Fakhri, Ph.D.
Rationale 2: AC & Motion artifacts in cardiac PET

Solution 2: Use Time-Dependent MR-based Attenuation Map according to event’s respiratory + cardiac motion phase

- Mismatched AC due to motion yields to false positive ischemia in the anterolateral myocardial wall.
Methods: Motion Corrected OSEM

- List-mode MLEM reconstruction algorithm with motion modeled in the system matrix:

\[ a_{ni}(f) = \sum_{j=1}^{M} a_{nj} \times m_{ji}(f) \]

Motion interpolation matrix (i.e., contribution of pixel i in the reference frame to pixel j in the deformed frame)

- Attenuation correction using deformed attenuation maps at each frame:

\[ \rho_i^{(a+1)} = \frac{\rho_i^{(a)}}{\sum_{f=1}^{F} s_i(f)} \times \frac{N}{\sum_{n=1}^{N} \sum_{j=1}^{M} a_{ni}(f_n) \rho_j^{(a)}} \]

Number of counts in list-mode

Motion dependent system matrix

- Transformation using measured motion fields from tagged MR

Attenuation map in the reference frame

Attenuation maps in the deformed frames

Ouyang J., Petibon Y., El Fakhri G.
Primate Results: Acquisition

• Motion Correction with *Primate* in simultaneous PET-MR

Gated tagged MR

Gated PET

Respiratory and cardiac motion is the most serious limitation to whole-body PET. Here, reconstructed PET images of a freely breathing monkey show that MRI-based motion correction in simultaneous PET/MRI increases contrast and resolution but does not increase noise. This results in significant improvement in PET image quality and is a compelling rationale for further evaluation in clinical studies.

See page 1291.

Chun S.Y., Reese T., Guerin B., Catana C., Zhu X., Alpert N., El Fakhri G. Tagged MR-based Motion Correction in Simultaneous PET-MR. JNM 2012; 1284-1291
Liver patient study (1/3)

Cine MRI (TrueFISP)

Respiratory Gated PET

Respiratory motion amplitude in the dome of the liver (~0.7-1.5cm).

Initial results in hepatic lesions (2)

- Estimated Motion via B-spline non-rigid image registration

\[ \hat{T} = \arg \min \left[ \Psi_{SSD}(I_{tar}, T I_{src}) \right] + \eta R(T) \]
Liver patient study (3/3)

18F-FLT PET/CT Tumor Heterogeneity is an Effective Biomarker in the Diagnosis and Staging of Lung Cancer

Guo N., Li Q., Yen G., El Fakhri G.
We assessed the clinical value of tumor heterogeneity measured with $^{18}$F-FLT and $^{18}$F-FDG as a biomarker for lung cancer diagnosis/staging, and compared the performance to SUV of both tracers using final pathology as gold standard.

$Heterogeneity = \frac{1}{N} \sum_{i} I_i(d) = \frac{1}{N} \sum_{i} \sum_{j \neq i} (x_i - \bar{x})(x_j - \bar{x})w_{i,j}(d)$

- $N$: number of voxels in ROI
- $\bar{x}$: mean over all voxels
- $x_i$: test voxel
- $x_j$: neighboring voxels
- $w_{i,j}(d)$: binary distance measurement kernel
• Conclusion:

$^{18}$F-FLT tumor heterogeneity has great potential to augment diagnostic accuracy and improve tumor staging in oncological practice.
Feraheme (ferumoxytol): A Nanoparticle Drug

Approved For Treating Iron Anemia @ 500 mg Fe/person (high iron dose) in US & Europe

Lee Josephson, Ph.D., Hushan Yuan PhD, Marc Normandin PhD, Moses Wilks PhD, Dustin Wooten PhD, Nicholas Guehl MS
Why Image Phagocytosis With $^{89}$Zr-Feraheme and PET/MR (Instead of Feraheme & MR) ?

<table>
<thead>
<tr>
<th></th>
<th>Feraheme/MR</th>
<th>Feraheme/PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Dose</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Tissue NP Quantitation</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Tissue NP Detection</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>
Imaging of radiolabeled nanoparticle

Overall diameter ~ 25 nm

Crystallographic Unit Cell

10 nm CMD
10 nm CMD
5 nm iron oxide

M Normandin, M Wilks, H Yuan, N Guehl, L Josephson
PET Monocyte Tracking: IV Injected $^{89}$Zr-Feraheme (FH) NPs

$^{89}$Zr-FH NPs In Plasma, Vascular Phase @ 0.5h

$^{89}$Zr-FH NP

Liver & Spleen Phagocytosis with Monocyte $^{89}$Zr-FH Loading Phase @ 4 h

$^{89}$Zr-FH NP

$^{89}$Zr-FH Loaded Monocyte

Liver & Spleen

$^{89}$Zr-FH Loaded Monocyte Trafficking Phase, To Spleen & Lymph Nodes @ 48h

Liver

Spleen

Plasma

Lymph Nodes

48 h

Liver & Spleen

Renal Node

0.5 h

Carotids

Heart

4 h

Axillary

Renal

Popliteal

Lumbar
Off Label Feraheme/MRI for Imaging Macrophages currently in clinical studies in normal, brain tumor and inflammation

**Diabetes Inflammation**
(Type I Progression)
NCT01710072/Gaglia

**CNS Inflammation**
Stroke, Mult. Scler., Surgery, Aneursym
NCT00659776/Neuwelt
NCT01710072/Hasan

**Brain Tumor Uptake**
NCT00103038 & NCT00660543/Neuwelt

**Myocardial Infarction**
NCT01323296/Newby

**Carotid Inflammation**
NCT01674257/Newby

**Lymph node metastases**
Pancreatic, prostate breast, thyroid
NCT00920023/Weissleder,
NCT00087347/Harisinghani
NCT01927887/Harisinghani

**Imaging FH Macrophage Uptake By MR**
Novel Cost-Effective, High-Performance Modular Detectors

- Laser Induced Optical Barriers (LIOB):
  - Each laser pulse in internally focused laser beam, locally changes the scintillator crystal structure and its index of refraction (optical barrier).
  - Densely packed optical barriers work as a reflecting surface similar to reflectors in mechanically pixelated arrays.
  - We pixelated LYSO:Ce and CsI:Tl scintillators with various pixel size and thickness.

Sabet H., Christensen M., El Fakhri G.
Ultra-high Resolution PET with DOI

Image courtesy of Dr. Ling Jian Meng
Outline

- Improving Lesion Detection Accuracy in Oncologic PET – MR
- Exploring Cardiac Structure & Function with PET – MR
- Neurology and Neuroscience
- Imaging Guidance & Monitoring in Radiation Therapy Planning
Cardiac Beating Phantom

In and out pressure from ventilator

Vent

Gel with bkg activity

Defect

Inflatable balloons

Hot “myocardium”

Tagged MR

PET
Cardiac motion correction phantom study (2)

(a) End-diastole (reference)

(b) End-Systole

<table>
<thead>
<tr>
<th>MRI</th>
<th>MRI / N-MC (3min)</th>
<th>MRI / Gated (3min)</th>
<th>MRI / F-MC (3min)</th>
</tr>
</thead>
</table>

Pig PET-MR perfusion study

Cardiac motion measurement

tMR-End-diastole  tMR-End-systole  Flurpiridaz PET

Infarct
Pig PET-MR perfusion study

Cardiac Gated (OP-OSEM)

MC-OP-OSEM

OP-OSEM

MC-PSF-OP-OSEM

MRI

Septum

Inferior wall

\[ \sigma = 51.1\% \]

\[ \sigma = 51.4\% \]

\[ \sigma = 52.0\% \]
Pig PET-MR perfusion study

Line profiles

Activity concentration

- MC-PSF-OP-OSEM
- MC-OP-OSEM
- OP-OSEM
- Gated-OP-OSEM

Septum +5%
Inferior wall +59%

+84%
Patient $^{18}$F-FDG cardiac PET-MR study

Cardiac motion measurement

tMR-End-diastole

tMR-End-systole

$^{18}$F-FDG PET
Patient $^{18}$F-FDG cardiac PET-MR study

Cardiac Gated OP-OSEM

OP-OSEM

$\sigma = 35.8\%$

PSF-OP-OSEM

Motion-Corrected MC-PSF-OP-OSEM

$\sigma = 32.8\%$

$\sigma = 35.8\%$

$\sigma = 36.6\%$
Rest-stress scan protocol followed before and after infarction of the LAD territory of pigs.

Kinetic model with time-varying parameters to estimate blood flow from the single scan rest-stress protocol (1). MGH2 model changes the flow abruptly when vasodilator is administered.
Single-scan rest/stress imaging with [18]flurpiridaz

A: $^{18}$F-Flurpiridaz images before and after infarction.

B and C: Fit from normal and infarcted segment respectively.

D: MBF at rest (RMBF) and stress (SMBF) as well as myocardial flow reserve (MFR) in healthy and infarcted area.
Mapping of membrane potential with TPP+

Membrane potential map of infarcted pig computed from a modification of the Nernst equation (1)

\[ \Delta \Psi (mV) = \frac{1}{\beta} \ln \left\{ \left( \frac{C_{PET}}{C_{plasma}} \right) \left( 1 - f_{xcell} \right) \right\} - (1 - f_{mito}) e^{\beta \Delta \Psi_{cyt}} \]  

N. Alpert, M. Normandin, N. Guehl, D. Wooten, L. Ptaszek, M. Moussa, G. El Fakhri
Outline

- Improving Lesion Detection Accuracy in Oncologic PET – MR
- Exploring Cardiac Structure & Function with PET – MR
- Neurology and Neuroscience
- Imaging Guidance & Monitoring in Radiation Therapy Planning
Brain motion correction using wireless MR active makers

Wireless Active Marker

Anatomical Prior: MAP framework to incorporate MR

$$\max_{f \geq 0} \log p(g | f) + \mu D(X, Y)$$

$$D(X, Y) = \sum_{i=1}^{N_f} D(X_i, Y_i)$$

$$D(X_i, Y_i) = I(X_i, Y_i)$$

$X_i, Y_i$: Random vectors corresponding to scale-space feature vectors extracted from the PET and anatomical images

$D(X_i, Y_i)$: Information theoretic similarity measure

$I(X_i, Y_i)$: Mutual information

Li, Dutta, Leahy, El Fakhri
PET reconstruction using MR “anatomical priors”

Siemens HD OSEM3D  MAP recon

MRI  Fused MAP PET & MR (Joint Entropy-Scale Priors)

Q. Li, IEEE TMI 2011
Subject with relatively low MMSE score. Tau aggregation originates in the entorhinal cortex and invades the temporal lobe as the disease progresses. In very advanced stages of the disease, it reaches frontal lobe. This patient with moderate AD exhibits prominent T807 uptake in the temporal lobe indicating a significant tau burden in that region.
Patient with a high MMSE score and noticeable T807 uptake in the hippocampus and the striatum. Note the distinction between the caudate nucleus and putamen with SVPDF-JE.
[F18]T807 Human Study

- ROIs: Whole brain, temporal lobe, inferior temporal gyrus, hippocampus, parahippocampal gyrus

Dutta, Johnson, Li, El Fakhri, SNMMI 2014, Saint Louis
PET Imaging of AD

- **Biomarkers for AD:**
  - Measures of amyloid: CSF Aβ and amyloid PET
  - Measures of neurodegeneration: FDG PET hypometabolism, MRI structural atrophy, CSF tau, tau PET
  - Cognitive decline loosely linked to amyloid, closely linked to neurodegenerative biomarkers

- **Updated pathophysiological model:**
  - *Tau pathology precedes Aβ deposition in time, but remains at a subthreshold biomarker detection level*

- **PET tracers for tau:**
  - [18F]FDDNP
  - [18F]THK523
  - [18F]T808
  - [18F]T807

Dutta, Johnson, Li, El Fakhri
Tau imaging with $[^{18}\text{F}]\text{T807}$

- Tau is a naturally occurring protein involved in microtubule structure
- Hyperphosphorylated tau oligomerizes to form insoluble filaments
- Converging evidence points to tau pathology in traumatic brain injury (TBI or CTE)
- We aim to study $[^{18}\text{F}]\text{T807}$ kinetics and use this tracer to image tau in subjects with CTE
*In vivo* binding of T807 in TBI
[\textsuperscript{18}F]T807 and tractography in TBI

M Normandin, D Wooten, W. Wedeen, R. Zafonte, N. Zucevik, G El Fakhri
$^{18}\text{F}]$T807 and tractography in TBI
Role of PET-fMRI in detection of neuromodulatory changes in specific neurotransmitter systems

**Brain activation paradigms**

+ Detect the loci of flow-related changes elicited by cognitive tasks
- Do not provide information about underlying neural mechanisms

**Neuromodulation paradigms**

+ Target specific neurotransmitter/Receptor
+ Pharmacological Challenge (e.g. Amphetamine/DA)
+ Cognitive task

Alpert, Normandin, Wooten, Guehl, El Fakhri
Explicit motor memory activates striatal dopamine system

Dopamine was released in the anterior part of the body of caudate (a,b) and in the dorsomedial putamen (a,c) during performance of an explicit motor memory task (t-maps: t > 3.0)

TAC show PET activity concentration for $^{11}$C-raclopride (D$_2$ receptor) in the anterior part of the body of the caudate and dorsomedial aspect of posterior putamen. PET activity in the reference region of putamen did not change significantly.

Alpert, Wooten, Guehl, Normandin
Simultaneous PET/fMRI to probe neurotransmission

- PET can measure receptor occupancy
- fMRI can measure neurovascular response elicited by receptor stimulation

Simultaneous PET/fMRI combines molecular specificity and temporal resolution

(Sander et al., PNAS 2013)
PET/MR: More than the sum of its parts?

Basic geometry of non human primate in PET-MR scanner

Photo of macaque just prior to imaging, including RF coils, infrared light source for eye tracking, etc.

Normandin, Alpert, Mandeville, Wooten, Guehl, El Fakhri
fMRI Signal Changes Appear Complex

Response to opiate agonist differs across regions

Response to dopamine agonist differs across regions

Response to amphetamine differs across regions and does not simply scale with dose

Liu et al., NeuroImage 2007

Choi et al., NeuroImage 2010

Ren et al., NeuroImage 2009
Proposed Kinetic Model of fMRI-CBV Responses to Dopaminergic Stimuli

\[
\frac{dD_1^{DA}(t)}{dt} = k_{on}^{D1} DA(t) \left[ D_{1\text{total}} - D_1^{DA}(t) \right] - k_{off}^{D1} D_1^{DA}(t)
\]

\[
\frac{dD_2^{DA}(t)}{dt} = k_{on}^{D2} DA(t) \left[ D_{2\text{total}} - D_2^{DA}(t) \right] - k_{off}^{D2} D_2^{DA}(t)
\]

\[
CBV(t) = \alpha_1 D_1^{DA} - \alpha_2 D_2^{DA}
\]

Mandeville et al., ISMRM 2012
Normandin et al., NRM 2012
Model predicts fMRI response to amphetamine
Unified PET/fMRI of neurotransmission

PET alone

fMRI alone

unified PET/fMRI

N Guehl, D Wooten, M Normandin
Simultaneous PET/fMRI to measure neurotransmission

Dopamine agonist binds to dopamine receptors (DARs)
- alters receptor occupancy resulting in a perturbation in the PET signal
- stimulates DARs resulting in changes in fMRI signal

The goal of this work is to synergistically combine the information provided by PET and fMRI to study neurotransmission. Ultimately this will provide a methodological framework with applications to studying brain signaling in people with mental health disorders and the action of drugs in substance abuse.

D.W. Wooten, et al., Center for Advanced Medical Imaging Sciences, MGH/HMS
Our work shows prototypical DA-D$_1$ antagonists do not elicit antagonist like behaviors

Baseline dopamine levels result in a partial agonist-like response from NNC112 (increase in CBV)

High levels of dopamine levels result in an antagonist-like response from NNC112 (decrease in CBV)

The partial agonistic properties of NNC112 are similar for SCH23390 calling into question the prototypical ‘D$_1$ antagonist’ and casts new light on the potential of D$_1$ for therapeutic applications

D.W. Wooten, et al., Center for Advanced Medical Imaging Sciences, MGH/HMS
Outline

• Improving Lesion Detection Accuracy in Oncologic PET – MR
• Exploring Cardiac Structure & Function with PET – MR
• Neurology and Neuroscience
• Imaging Guidance & Monitoring in Radiation Therapy Planning
PET-MRI for clinical target volume definition in RT planning for Soft Tissue Sarcoma

- Peritumoral edema for STS can extend up to 4 cm from the T1 gross tumor
- Current RTOG concensus for STS clinical target volume for high grade STS
  » 3.5 cm longitudinally
  » 1.5 cm radially
- Additional T2 suspicious edema would be added to the expansion
- However, some lesions are associated with very extensive T2 abnormalities
- Can we better define the amount of suspicious peritumoral edema to include for preop RT clinical target volume using PET-MRI?

Zhang X., Chen Y.L., Lim R., El Fakhri G.
PET-MR in Radiation oncology treatment planning

Soft Tissue Sarcoma (STS)

Zhang X., Chen Y.L., Lim R., El Fakhri G.
PET-MR in Radiation oncology treatment planning

Soft tissue sarcoma

T1w MR

PET

Simultaneously acquired PET-MR
PET-MR in Radiation oncology treatment planning

Soft tissue sarcoma

Before

After

Zhang X., Chen Y.L., Lim R., El Fakhri G.
PET before treatment

SUV > 15
PET after treatment

SUV=5

SUV=2
In the tumor voxel (4x4x4cm³), the choline/lipid ratio is 4 times higher than normal tissue voxel.

Zhang X., Chen Y.L., Lim R., El Fakhri G.
Conclusions: PET–MR: Opportunities in the Clinical Setting & Beyond

- **Exciting times** in oncologic, brain and cardiac PET-MR (not just engineering but radiochemistry, clinic as well)!

- Synergistic role for PET-MR-MRS-CT in **radiotherapy** planning, PET/fMRI for finally **mapping neurotransmission**, in cardiac mapping of **membrane potential**, MC-1 and perfusion, and in **dual PET-MR probes**

- Unique Opportunity for better understanding of **Molecular Physiology Through Imaging**

G. El Fakhri, Ph.D.