Mechanistic Neuroimaging: The New New New Thing

A. Gregory Sorensen, M.D.

Siemens Healthcare
North America

Disclosures:
Research Funding:
NIH AstraZeneca Genentech Merck Novartis Schering-Plough Siemens Takeda

Consulting:
Breakaway BMS Epix Biogen Bayer Schering-Plerging Merrimack Mitsubishi Olea GE Healthcare Regeneron Genentech AstraZeneca Novartis Takeda

Equity: Catalyst Medical
Outline

• Introduction: Imaging and Value-based Healthcare

• Mechanistic Imaging
  – What is it?
  – Example: The controversy around Avastin (bevacizumab)

• One New Method: MR-PET
  – Recently FDA-approved
  – Easy reimbursement
  – Opportunities for mechanistic imaging throughout the body
Physicians value diagnostic tools

Dartmouth-Stanford Survey of Medical Innovations

Q: How important is this innovation to your practice?

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<td>0.591</td>
<td>23.6 71.1 5.3</td>
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<td>14</td>
<td>Laparoscopic surgery</td>
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<td>20.9 69.8 9.3</td>
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<td>NSAIDs and Cox-2 inhibitors</td>
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<td>Cardiac enzymes</td>
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<td>Fluoroquinolones</td>
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<td>6.7 84.0 9.3</td>
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<td>Recent hypoglycemic agents</td>
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<td>12.9 69.8 17.3</td>
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<td>19</td>
<td>HIV testing and treatment</td>
<td>0.444</td>
<td>15.6 87.8 26.7</td>
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<td>20</td>
<td>Tamoxifen</td>
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<td>3.1 81.8 15.1</td>
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<td>26</td>
<td>Calcium channel blockers</td>
<td>0.291</td>
<td>1.8 54.7 43.6</td>
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<td>27</td>
<td>IV-conscious sedation</td>
<td>0.289</td>
<td>1.8 54.2 44.0</td>
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<td>28</td>
<td>Sildenafil (Viagra)</td>
<td>0.256</td>
<td>0.9 49.3 49.8</td>
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<td>29</td>
<td>Nonsedating antihistamines</td>
<td>0.231</td>
<td>1.3 43.6 55.1</td>
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<td>30</td>
<td>Bone marrow transplant</td>
<td>0.182</td>
<td>1.3 33.8 64.9</td>
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Fuchs and Sox, Health Affairs 2001 20(5):30-43
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## Mean Response And Ranking Of Physicians’ Ratings Of Innovations, 2001

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Boundaries: White matter and pial surfaces

Gray-white boundary

Pial surface

Courtesy Anders Dale, Bruce Fischl, MGH
Representing the pial surface

Gray-white boundary

Pial surface

Courtesy Anders Dale, Bruce Fischl, MGH
Inflation via “relaxation”

Courtesy Anders Dale, Bruce Fischl, MGH
Cortical Thinning with Aging
Cortical Thinning with Aging
Cortical Thinning with Aging
Pre-Term and Newborn Growth Model

Bruce Fischl, Peng Yu, Evelina Busa, Rudolph Pienaar and Ellen Grant
Selective Regional Thinning in AD

Lateral
- Prefrontal Cortex
- Central Sulcus/Precentral Gyrus

Medial
- Prefrontal Cortex
- Central Sulcus/Precentral Gyrus
- Posterior Parahippocampal

Ventral
- Prefrontal Cortex
- Central Sulcus/Precentral Gyrus
- Entorhinal Cortex

Dorsal
- Prefrontal Cortex
- Central Sulcus/Precentral Gyrus
- Parietal Cortex
What is Mechanistic Imaging?

• Advanced imaging focused on specific pathophysiologic questions and pathways

• Can be molecular, structural, functional, (including “big F” Functional) etc.

• Context and pathway understanding can be more important than technique!
One possible topic: The mystery of anti-angiogenic therapy

- Doesn’t seem to kill tumor on its own
- Only seems to work with another traditional (cytotoxic) agent
- No dose-response relationship
- What is going on?
Antiangiogenic therapy:

Effect on Contrast Enhancement

J. Vredenburgh
Duke

Clin Canc Res
2007 13:1253
Antiangiogenic therapy: Effect on Contrast Enhancement

J. Vredenburgh
Duke
Mechanistic Imaging in Malignancy

- Investigating Anti-angiogenesis and the “vascular normalization” hypothesis

Jain, Science 2005 307:61
Mechanistic Imaging in Malignancy

- Investigating Anti-angiogenesis and the "vascular normalization" hypothesis

Jain, Science 2005 307:61
Mechanistic Insights from MRI

• Testing the “Vascular Normalization” hypothesis

• Blocking VEGF should result in:
  – Smaller vessels
  – Less permeability
  – Less edema
  – Decreased mass effect
  – Probably no survival benefit without combination therapy, though…
Mechanistic Insights from MRI

• Testing the “Vascular Normalization” hypothesis

• Blocking VEGF should result in:
  – Smaller vessels
  – Less permeability
  – Less edema

Vascular Normalization after Anti-angiogenic treatment
Winkler et al, Cancer Cell 2004
Vessel Caliber Imaging (VCI) with MRI

• Initially described in 1998 by MGH group with histological validation (Dennie et al, MRM 1998)

• Studied by multiple other groups
  – Baddrudoja et al, Neuro-Oncology 2003, with histological validation
  – Pathak et al, Mag Res Med 2001, with histological validation
  – Tropes et al, MRM 2001
  – Jensen et al, MRM 2000
Physics of Mean Vessel Caliber

Ratio of $\Delta R2^*/\Delta R2 \approx$ average vessel size in voxel
Gradient Echo versus Spin Echo EPI: simultaneous acquisition approach

3.0 Tesla, TR 1.5s, TE for GE: 28, TE for SE: 105
0.2 mmol/l Gd-DTPA.
**GE vs SE**

**DSC**

Pilocytic astrocytoma

4.4 : 1 tumor/white on GE

vs 1.75 : 1 tumor/white on SE

M Pescitides / Martinos - MGH - HST
Evidence of Vascular Normalization with VEGF blockade (AZD2171, cediranib)

Post-contrast T1-weighted MRI

Relative Vessel Caliber

Supported by US PHS Grant R21-CA117079
Anti-Angiogenic Drug Effects: Decreased Permeability + Edema

Permeability ($K_{\text{trans}}$)

T2 weighted MRI (FLAIR)

Water Mobility (ADC)
Re-emergence of White Matter Tracts

Day -1  Day +27
A Window for Vascular Normalization?

Pt #11  -6            -2                 +1                +28               +72

Post-contrast T1-weighted MRI

Relative Vessel Size

T2-weighted MRI (FLAIR)
Evidence of Vascular Normalization Window with VEGF blockade

**T1 post Gd Volume over Time**

- Plot showing T1 post Gd volume over time with different patient markers.

**Normalization**

- Graph showing value relative to pretreatment over study days.

Supported by US PHS Grant R21-CA117079

3T TimTrio

Batchelor+Sorensen, Cancer Cell 2007
A “Vascular Normalization” Index: $K_{\text{trans}} + \text{CBV} + \text{Collagen IV}$

Sorensen et al, Canc Res 2009
A “Vascular Normalization” Index: $K_{\text{trans}} + \text{CBV} + \text{Collagen IV}$

Sorensen et al, Canc Res 2009
Bevacizumab - FLT PET vs. MRI
Bevacizumab - FLT PET vs. MRI

J Clin Oncol
2007
25:4714-4721
Key Innovation: Avalanche Photodiodes

B ≠ 0

Crystal profiles
Key Innovation: Avalanche Photodiodes

- Consists of:
  - Four 8 x 8 arrays of 2 x 2 x 20 mm LSO crystals read out by 16 APDs (Hamamatsu)
  - Two 10 channel charge-sensitive preamplifiers (Concorde MicroSystems)
  - Temperature stability with compressed air
Integrated MR-PET Scanner: Installation
Whole-body MR-friendly PET architecture
Initial installation at MGH of fully-integrated whole-body MR-PET

Front

Back (with cover off)
First Volunteer MR-PET (FDG) Scan
Simultaneous MR-PET Data Acquisition

54 year old with malignant glioma and cutaneous extension

5.45 mCi FDG injected approx. 2.5 hours prior to data acquisition
OSEM 3D reconstruction
Attenuation correction performed based on the MR data

T1 MP-RAGE, T2 SPACE (shown), FLAIR, DTI, CSI, SVS sequences run simultaneously
CP coil
Simultaneous Acquisition of MR and PET Allows for Rich Data Collection

- PET
- PET+ MR
- High Res Anatomy
- Diffusion Tractography
- Surface Rendering
- MRA
Tumor hypoxia – simultaneous MR & FMISO-PET

Day -1

Day +1

Day +50
What can PET and MR do for each other?

**PET:** molecular specificity

**MR:**
- Anatomy
- Attenuation Correction
- Motion Correction
- Arterial Input Function Estimation
Advantages of Simultaneity

• Convenience for patient
  – Some 15-20% of our PET patients get MR anyway

• Throughput

• Improved coregistration
  – Real-time motion correction
  – Better partial volume correction

• Quantification
  – Arterial input functions, etc.

• Smart probes / contrast agents
2011 Applications For MR-PET In The Body

- Pediatric PET applications
- Pelvic oncology
  - CT doesn’t do so well in the pelvis
- Breast oncology
  - Co-registration in breast not always easy
  - MRI has high sensitivity but modest specificity
- Cardiac
  - Only want to give chemical or physical stress once
- Lymphoma
  - “Frequent flyer” young patients can reduce dose via MR
2012 Applications For Simultaneous MR-PET In The Body

- With complex organ motion correction:
  - Lung
  - Cardiac
  - Liver
  - Kidney

- Replacing the blood arterial input function with image-based AIF
Why MR-PET?

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

Thanks to Luiz Celso Hygino da Cruz, Romeu Côrtes Domingues
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Coming soon:
AV 45
florbetapir

JAMA 2011
305(3):278

Sagittal and axial views of positron emission tomographic (PET) scans of representative patients. The vertical bars indicate the range of semiautomated quantitative analysis of the ratio of cortical to cerebellar signal (SUVR) scores. The maximum color (red) corresponds to an SUVR of approximately 2.2. The 4G8 immunohistochemistry shows prefrontal gray matter with aggregated β-amyloid (red) using a 3-ami-no-9-ethyl-carbazol chromogen stain and counterstained with acid blue 129 (original magnification X5).
MRI in AD -- ADNI data


83% Sensitivity
93% Specificity
in 175 patients with MCI

Average differences in thickness for subjects with AD and MCI relative to HC (NC)

Simultaneous MR-PET in Alzheimer’s Disease

Comparison of the MR and PET data with a healthy control population (p<0.05)

Alexander Drzezga, Brad Dickerson, Ciprian Catana, MGH
Conclusions

- Mechanistic Imaging: A new way to think about how to answer the most important questions

- Novel methods are not required, but can be helpful

- Innovation still abounds in radiology
Acknowledgements

- Ciprian Catana, Bruce Rosen, Georges al-Fakhri, Nat Alpert, Tracy Batchelor, Rakesh Jain, Larry Wald, and many students, faculty, and staff at MGH

- The mMR team at Siemens

Special Thanks to:

Elizabethh Gerstner  Dan Chonde  Heisoog Kim  Grae Arabasz
Ona Wu  Grace Kim  Spencer Bowen  Michael Hamm
Thomas Benner  Bill Copen  Ronald Borra  Marco Pinho
Nicki Jennings  Rita Polischuk  Ruopeng Wang  Jacob Hooker
Kyrre Emblem  Philip Z Sun  Chan Gyu Choo  Van Wedeen
Hakan Ay  Andre Van der Kouwe  Weiting Zhang
Ovidiu Andronesi  Christin Sander  Nancy Shearer  Krista Fariel

and many, many more...