Why Image?

- The Nature of the Universe
  - Spatially Heterogeneous
- Human Nature
  - Seeing is Believing
“White on White”

Robert Rauschenberg, 1951

HUP

2003
SEEING IS BELIEVING...

University of Pennsylvania

Imaging Sciences Program
The Power of Imaging
An Image

• Spatially coherent display of local measurements of mass or energy (Signals).
  – As a function of time

• Necessary for studying spatially heterogeneous objects
  – Patients
  – Diseases
  – Especially important for the brain and its diseases
The Traditional Total Body Scanner

John R. Stanley, M.D.
Milton B. Hartzell Professor of Dermatology
Chairman
Medieval Medical Imaging
Dr. Wilhem Conrad Roentgen

Jan 1896
Skull Film
NeuroImaging 1974
Imaging No Brain

1896

1919

1937

1964
NeuroImaging 1985
Imaging a Brain

1975

1983
Historical Perspective

• Indirect Imaging of Brain
  – Babinski Sign

• Direct Imaging of Brain
  – Anatomic
    • Post Mortem
      – Autopsy
    • Pre Mortem
      – CT
  – Physiological/Biochemical
    • Radionuclide Scans
Indirect Functional Imaging
Categories of Brain Imaging

- Anatomical Imaging
  - Static morphology
- “Dysfunctional” Imaging
  - Combination of:
    - Morphological Imaging
    - Measure of Function
  - Indirect Imaging of Function
- Functional Imaging
  - Physiological or Biochemical Imaging
    - Adynamic at Rest
    - Dynamic with Task
Anatomic Imaging
Model Brain
Anatomic Imaging
My Brain
“Dysfunctional” Brain Imaging
Lesion Deficit Correlation

Broca, 1896

C/o G. Salamon
“Dysfunctional” Brain Imaging

M. Kraut, 95
Functional Units of the Brain

- Neurons
  - Post-synapse
  - Dendrites
  - Cell Body
  - Axon
  - Pre-synapse
- Glia
- Neuron Ensembles
  - Nuclei
  - Cortical Fields

Functional Signals of the Brain

- Physiological
  - Electrical
  - Blood flow
- Molecular
  - Neurotransmitters
  - Metabolism
Functional Imaging Techniques

- Physiological
  - Electromagnetic
    - EEG
    - Magnetoencephalography
  - Cerebral Flow
    - Spect/PET
    - MRI
    - CT
    - Optical
Functional Imaging Techniques

• Biochemical
  – Bioenergetic
    • PET
      – FDG
      – O2
    • MRS - lactate
  • BOLD MRI
  • Optical
  – Molecular
    • Spect/PET
    • MRS
EEG Maps

Finger Tapping

Green, et al, 1999
Magneto Encephalography
Tonotopic Localization

Lauter, et al; 1996
Molecular Imaging

FluoroDopa uptake and Raclopride binding in Right hemi—Parkinsonism

FluoroDopa
Raclopride
Normal
Parkinson's Disease
MSA

Sawle, et al; 1995
Functional Brain Imaging

• “It is more important to know what the brain is doing than what it looks like.”
  – Historical Perspective
  – Categories of Brain Imaging
  – Functional Units of the Brain
  – Functional Imaging Techniques
Cerebral Bioenergetic Metabolism

- **Purpose:** Generate ATP
- **Dependent on Neurophysiological Activity**
  - Greatest in Active Gray Matter
- **Mechanisms**
  - Anaerobic
    - ? Conditions
    - Requires glucose
  - Aerobic
    - Requires oxygen and glucose
Cerebral Blood Flow

• Purpose: Deliver Bioenergetic Substrates
  – Dependent on Metabolic Demand
  • Indirectly Dependent on Neurophysiological Activity
  • Mechanisms
    – Unknown
    – ? Nitric Oxide
Cerebral Metabolism and Blood Flow
Resting State
Cerebral Bioenergetic Metabolism

Glucose

1. Hexokinase
2. Phosphofructokinase
3. Pyruvate Kinase

Glycolytic Pathway

Glyceraldehyde-3-Phosphate

Phosphoenolpyruvate

Pyruvate

Anaerobic

Glycolytic Enzymes

1. Hexokinase
2. Phosphofructokinase
3. Pyruvate Kinase
Cerebral Metabolism

Pyruvate $\rightarrow$ Lactate

Acetyl CoA $\rightarrow$ Citrate $\rightarrow$ Isocitrate $\rightarrow$ $\alpha$-Ketoglutarate $\rightarrow$ Succinyl CoA $\rightarrow$ Succinate $\rightarrow$ TCA

Glucose + 36 ADP + 6 O$_2$ $\rightarrow$ 6CO$_2$ + 36 ATP + 42 H$_2$O

Aerobic
Cerebral Metabolism and Blood Flow
Active State
Cerebral Bioenergetic Metabolism

**Glucose**

1. **Hexokinase**
   - ATP
   - ADP

2. **Phosphofructokinase**
   - ATP
   - ADP

**Glycolytic Pathway**

1. **Glyceraldehyde-3-Phosphate**
   - NAD+
   - NADH
   - ADP
   - ATP

2. **Phosphoenolpyruvate**
   - ADP
   - ATP

3. **Pyruvate**
   - ADP
   - ATP

**Activated Anaerobic**

**Glycolytic Enzymes**

1. Hexokinase
2. Phosphofructokinase
3. Pyruvate Kinase
Cerebral Metabolism

Glucose + 36 ADP + 6 O2 → 6CO2 + 36 ATP + 42 H2O

Activated Aerobic

Pyruvate → Lactate

Acetyl CoA → Citrate → Isocitrate → Δ-Ketoglutarate → Succinyl CoA → ATP

Oxaloacetate → TCA

Succinate → ATP

Citrate → ATP
Functional PET Imaging

Fox, et al, 1985
MR Spectroscopy

Normal Human Brain

NAA

Cho

PPM 3.0 2.0 1.0

PPM 3.0 2.0 1.0

PPM 3.0 2.0 1.0
BOLD and Glutamate Hypothesis

Raichle; 2001
fMRI BOLD Signal

INCREASED NEURAL ACTIVITY

RELATIVELY DECREASED VENOUS DEOXYHgb

RELATIVE INCREASE IN SIGNAL

BLOOD FLOW

O₂ UPTAKE

INCREASED VENOUS O₂ CONTENT

DECREASED LOCAL SUSCEPTIBILITY EFFECT

DECREASED SPIN DEPHASING

INCREASED NUMBER OF INFLOWING SPINS

Kraut, 1995
fMRI Box Car Design

Reference Function

MRI Signal

Time (seconds)

\[ t = \frac{A}{\sigma_A} \]

A

Slope

\( \Phi \)
Visual Activation: $\text{H}_2\text{O}^{15}$ PET

Visual Activation: Functional MRI

**Cognitive Task Design**

*Scene Encoding Task*  
*Control Task*

Subjects viewed 60 complex visual scenes at a rate of one every 4 seconds, and were instructed to remember them for a forced-choice recognition test following the scan.

The control condition for the visual scene encoding task required subjects to attend to an equal number of randomly pixelated control images presented at the same rate as the complex scene images.

Control images were presented during six 40 second blocks that alternated with the scene stimulus encoding blocks.

Detre, et al, 1999
Functional MRI

Scene Memory

P = .005

Sentence Memory

Functional MRI

Scene Memory

Sentence Memory

P = .05

Functional MRI

Scene Memory

Sentence Memory

fMRI and Post Surgical Deficit
Finger Tapping; Brain Tumor

Ulmer, et al; 1999
Cerebral Metabolism and Blood Flow
Ischemia
Cerebral Metabolism and Blood Flow
Neoplasia
L Hemiparesis

6 Hours
Right Internal Carotid Occlusion
Subtracted GRASS Images
MR Perfusion: Occluded R ICA
MR Perfusion: Occluded R ICA

TTP

CBV
MRS: Occluded R ICA

6 Hours
MRS: Occluded R ICA

T1 MR
NAA MRS
Lactate MRS
6 Hours
Occluded R MCA

8 Days
Dynamic Contrast Enhanced GRE Perfusion Imaging

- Grade I Glioma
- Anaplastic Glioma
- Glioblastoma

Cha, et al; Rad. 2002
MRS Glioblastoma
Mouse Imaging

MRI Cardiac Wall Motion

Optical P53 Gene Expression
Mouse Brain Imaging

Serotonergic SPECT
[99mTc]TRODAT(II)

Striatum

Mutant
Wildtype

EMX-1 Mutation

Difference Image