Principles of Neuroimaging

Positron Emission Tomography (PET) Applications

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What is Positron Emission Tomography (PET)?

*Tomograph is a picture of a slice*

**Positron emission:**
- Positron leaves atomic nucleus.
- Annihilation of positron and electron.
- Coincidence events detected

**Computer system reconstructs image of annihilations.**
This shows where radioactive tracer accumulated.
Molecular Brain Imaging

- Psychology
  - Experimental Design
- Nuclear Medicine
- Physiology/Pharmacology
- Physics
- Chemistry
- Mathematics
  - Computer Sciences
Goals of Molecular Imaging

**Research:**
Figure out how the brain works.
What circuits are activated or de-activated?

Characterize illness.
What circuits? What transmitter systems?

Advance treatment.
Rational basis to design therapies.
Evaluate treatments.

**Clinical:**
Diagnosis & evaluation of disease progression/recovery
What Can You Measure?
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- Indices of regional brain function:

  *blood flow, glucose metabolism, O₂ metabolism*
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• Proteins of interest:
  neurotransmitter receptors, transporters
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• Neurotransmitter turnover
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• Dynamic changes in neurotransmitter function with cognition?
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• Neurotransmitter release
• Neurotransmitter turnover
• Dynamic changes in neurotransmitter function with cognition – to some extent
**PET vs. SPECT**

**PET – decay by emission of positrons**
(photons released as byproducts)
short-lived isotopes – cannot be shipped
   O-15 (2 min) C-11 (20 min)
   F-18 (110 min)
   Br-76 (16.2 h), N-13 (9.97 min)
advantage of C-11-- many compounds possible

**SPECT – decay by single photons**
long-lived isotopes – can be shipped
   I-123 (13.3 h), TC-99m (6.01 h), In-111(67 h)
more commonly used clinically
SPECT Tracers

Cerebral Blood flow:

\[ ^{99m}Tc\text{-HMPAO}, \ ^{123}I\text{lodoamphetamine} \]

D2-like Dopamine Receptor:

\[ \ ^{123}I\text{lodosobenzamide, } \ ^{123}I\text{epidipride} \]

Dopamine transporter:

\[ \ ^{123}I\beta\text{-CIT, } \ ^{99m}Tc\text{TRODAT} \]

Serotonin transporter:

\[ \ ^{123}I\text{ADAM, } \ ^{123}I\beta\text{-CIT} \]

Nicotinic Acetylcholine Receptor

\[ \ ^{123}I\text{5-Iodo-A-85380} \]
Development of PET

PET III built in 1974 - Washington University

M. Ter-Pogossian  E. Hoffman  M. Phelps
Functional Imaging with PET

The brain uses glucose and O2 for energy.

Cerebral Glucose Metabolism

[F-18]fluorodeoxyglucose

Cerebral Blood Flow

[O-15]Water

Used less often:
O-15 -- oxygen metabolism
[C-11]O -- cerebral blood volume
[C-11]acetate – brain tumors
Beginning of Metabolic Mapping
The Deoxyglucose Method

L. Sokoloff

THE $[^{14}C]$DEOXYGLUCOSE METHOD FOR THE MEASUREMENT OF LOCAL CEREBRAL GLUCOSE UTILIZATION: THEORY, PROCEDURE, AND NORMAL VALUES IN THE CONSCIOUS AND ANESTHETIZED ALBINO RAT

J. Neurochemistry, 1977
Quantitative Autoradiography Preceded PET

Opioid Agonist Effects in Thalamus

Saline

Nalbuphine (κ agonist)

Morphine (μ agonist)

Oxymorphone (μ agonist)

V = ventral posterior n.
G = gelatinosus n.

L. Sokoloff et al., 1977

RF Fanelli et al., 1987
Adapting the Deoxyglucose Method for PET

$[^{18}\text{F}]$Fluorodeoxyglucose Synthesis 1976


*J. Labeled Compounds and Radiopharm.*, 1978


*J. Labeled Compounds and Radiopharm.*, 1978
[\textsuperscript{18}F]Fluorodeoxyglucose

\[ E = mc^2 \]
Tracer Kinetic Models

*a mathematical framework for calculating rates of biological processes with PET*

- Compartmental models - most common.
- Simplifications of biological systems.
- Formulated by differential equations describing exchange between compartments.
- Describe biochemical systems
- Require:
  - *extensive biochemical studies to define them*
  - *simplifying approximations in their practical formulations.*
FDG Model for Assay of Cerebral Glucose Metabolism

Diffusible, $\beta^+$-emitting Substrate is Converted to a Sequestered Product

The enzyme product is retained in cells. It accumulates in proportion to glycolytic rate.
Operational Equation for Calculating Cerebral Glucose Metabolism, FDG Method  

\( R_i \), rate of tracer incorporation

\[
R_i = \frac{C_p\left( C_i^* (T) - \frac{k_1^*}{\alpha_2 - \alpha_1}\left[ (k_4^* - \alpha_1)e^{-\alpha_1 t} + (\alpha_2 - k_4^*)e^{-\alpha_2 t}\right] \otimes C_p^*(t) \right)}{LC \left( \frac{k_2^* + k_3^*}{\alpha_2 - \alpha_1} \right) (e^{-\alpha_1 t} - e^{-\alpha_2 t}) \otimes C_p^*(t)}
\]

(replacing arterial with venous sampling as in original Sokoloff 1977 method)

See ME Phelps et al., Ann Neurol., 1979 for derivation and definition of terms.
Visual Activation (FDG)

Resting Brain

Viewing a Complex Scene
FDG PET Shows Disease-Related Dysfunction

Cortical Hypometabolism in Schizophrenia

Healthy control

Schizophrenic

altered metabolic relationship between frontal cortex, striatum & thalamus
$[^{18}F]FDG$ Reveals Cortical Deficit in Glucose Metabolism Bipolar and Unipolar Depression

**Bipolar Depression**
- colors indicate areas of lower glucose metabolism vs. control

**Unipolar Depression**
- colors indicate areas of lower glucose metabolism vs. control

Hosokawa et al., 2009
FDG PET Shows Neural Correlates of Behavioral State

Limbic activation accompanies cocaine craving

E. London, NIDA

Questions about Circuitry Asked with PET

- Studies at rest: What circuitry contributes to dysphoric mood? To pathology of OCD? To Cognitive decline in Alzheimer’s disease?

- Activation Studies: What circuitry is involved in a certain cognitive function?

- Drug challenge studies: What regions/circuits are affected by a drug treatment?

Better with fMRI?
Yes, for cognitive challenge. No, for drug challenge if drug affects vasculature directly.
When to use PET Instead of fMRI for Functional Imaging

Frontal FDG-PET activity correlates with cognitive outcome after STN-DBS in Parkinson disease

Postoperative changes of verbal fluency correlated with nCMRGlC alterations in the left DLPFC (BA46: $r = 0.90$, $p = 0.001$)

With nCMRGlC in left Broca area (BA 44/45: $r = 0.85$, $p = 0.004$)

First Dopamine PET Scan 1983


H. Wagner                                           D. Wong

Questions about neurotransmitters

- How is dopaminergic (serotonergic, etc.) function different in the disease state?
  - Does a neurotransmitter parameter relate to severity of disease?
- Does a drug reach the intended receptor target?
- In disease, is the presynaptic element working?
  - How does a challenge that interacts with the presynaptic element (e.g., amphetamine) affect synaptic transmitter dynamics?
- How do such questions relate to function (mood, cognition)?
Radiolabeled Receptor Ligand

Depends on specific binding
  high affinity, low capacity
  (Nonspecific binding is low affinity, high capacity)

Generally -- Radioactivity in early scans depends on blood flow (distribution).
Radioactivity in later scans due to specific binding.
Unbound radioactivity and nonspecific binding have shorter residence in tissue.
Dopamine-Related PET Probes

Postsynaptic receptors:
- D2/D3 striatal: \([\text{C-11}]\)NMSP, \([\text{C-11}]\)raclopride
- D2/D3 striatal and extrastriatal: \([\text{F-18}]\)fallypride, \([\text{C-11}]\)FLB-457
- D3: \([\text{C-11}]\)PHNO
- D1: \([\text{C-11}]\)SCH23390, \([\text{C-11}]\)NNC-112

Transporters:
- \([\text{C-11}]\)methylphenidate, \([\text{C-11}]\)cocaine

Enzymes:
- \([\text{C-11}]\)deprenyl, \([\text{C-11}]\)clorgyline

Neurotransmitter Turnover:
- \([\text{F-18}]\)fluoroDOPA
Non-Dopamine PET Probes

Monoamines in General

Vescicular monoamine transporter: $[^{11}\text{C}]$DihydroTBZ

Monoamine oxidase A: $[^{11}\text{C}]$Clorgyline

Monoamine oxidase B: $[^{11}\text{C}]$Pargyline and $[^{11}\text{C}]$L-deprenyl (Selegiline)

Serotonergic System

5-HT$_{1A}$ receptor: $[^{11}\text{C}]$WAY-100635, $[^{18}\text{F}]$MPPF

5-HT transporter: $[^{11}\text{C}]$McN5625, $[^{11}\text{C}]$DASB

Cholinergic Systems

Nicotinic acetylcholine receptors: $[^{18}\text{F}]$A-85380

Muscarinic acetylcholine receptors: $[^{18}\text{F}]$FP-TZTP

Acetylcholinesterase: MP4A  Butyrylcholinesterase: MP4B

Metabotropic Glutamate Receptors

$m\text{GluR1}$: $[^{18}\text{F}]$MK-1312

$m\text{GluR5}$: $[^{11}\text{C}]$ABP688, 18F]F-PEB

Others: Benzodiazepine receptors
Selective Radiotracers in PET

• static neurochemical measures
• neurotransmitter dynamics
Receptor Binding

$$B = B_{max} \times \frac{F}{K_D} + F$$

$$F = \text{free ligand}$$

In plasma – Measure free ligand concentration directly (metabolite correction).

In brain – Measure radioactivity after calibration (phantom). Model distinguishes free from bound radioactivity.
**Binding Potential: Receptor Availability**

*The Logan Method*

\[ \text{Slope} = \text{DVR} = \text{BP} + 1 \]
Static Measure:

$[^{11}\text{C}]d$-threo-Methylphenidate

in Methamphetamine Abusers

The transfer constant of $[^{11}\text{C}]d$-threo-methylphenidate from plasma to brain ($K_1$) and the distribution volumes (DV) were calculated by tracer-kinetic modeling.

• No differences in $K_1$ between short vs. protracted abstinence.

• Increased binding to DAT in striatum (not cerebellum).

• DAT recovery was negatively correlated with amount and years of METH use.

Abuse severity may limit recovery.

Addiction: Low D2-like Receptor Availability
Addiction: Low D2-like Receptor Availability

Is it all about receptor density?
Raclopride in the Striatum: Effect of Endogenous DA on Binding Potential

\[ ^{11}C \]Raclopride

Placebo \quad \alpha - \text{Methylparatyrosine}

Decreased DA synthesis \quad \text{less competition from endogenous DA}

enhanced radiotracer labeling.
To What Extent is BP Affected by Endogenous Dopamine?

Percent Change in $^{[11}C$Raclopride Nondisplaceable BP for Cocaine-Dependent and Healthy Control Subjects After AMPT

D. Martinez et al., Am. J. Psychiatry, 2009
Neurotransmitter Dynamics

\[^{11}\text{C}]\text{raclopride in the Striatum: Measuring changes in Intrasynaptic DA}

Block DA reuptake → more competition from endogenous DA (depending on release) → reduced radiotracer labeling.
Studies of Cocaine Craving Use Videotapes with Images that Remind the Participant about Cocaine
The Participant Scores Cocaine Craving During PET Scanning

[¹¹C]Rclopride -- radiotracer for D2/D3 DA receptors

Cocaine-related cues

D2/D3 DA receptors visualized with PET
Cocaine Craving and Dopamine Release

Studies of $[^{11}\text{C}]$Raclopride Binding to D2/D3 DA Receptors

The maps below show striatal regions where DA release was related to craving.

Dopamine release in dorsal striatum is correlated with craving.

Participants who craved the most had the most DA release (largest change in DA receptor occupancy)

D.F. Wong et al. Neuropsychopharmacology, 2006

N.D. Volkow et al., J. Neurosci., 2006
Mu Opioid Receptor Binding is Correlated with Nicotine Dependence and Reward in Smokers

PET to Predict Treatment Outcome

D2/3 Receptor Binding Measured with $[^{11}\text{C}]$raclopride
Dopamine Release Assessed with Methylphenidate

D. Martinez et al., 2011
PET Used to Determine Therapeutic Regimen

Kapur & Seeman
Dopamine synthesis involves two major enzymatic steps.
[\textsuperscript{18}F]FDOPA is taken up into the presynaptic terminal, and is converted to [\textsuperscript{18}F]DA.

[\textsuperscript{18}F]FDOPA data reflect DOPA decarboxylase activity & DA storage.
FDOPA kinetics follows a 5-compartment model

Peripheral conversion of plasma FDOPA to 3-OMFD

FDOPA kinetics in striatum

Plasma FDOPA

Plasma 3-OMFD

Plasma FDOPA

Plasma 3-O-MFD

Extra-vascular 3-O-MFD

Tissue FDOPA

Tissue 3-O-MFD

FDA & metabolites

K_1

K_1^M

K_2

K_2^M

K_3
Slope of the Patlak Plot is the estimated FDOPA $K_i$. 
Measurements of Uptake or Influx of FDOPA

- ratio of specific /nonspecific uptake (region of interest $^{18}$F - occipital $^{18}$F)/ occipital $^{18}$F

- Determination of $^{18}$F-FDOPA influx constant ($K_1$ or $K_i$) calculated with a multiple time graphical analysis method
Loss of Nigrostriatal Innervation
[F-18]Fluorodopa and PET

Healthy Control

Parkinson’s Disease
Selective PET Tracers Other than Neurotransmitter and Metabolism Probes

- Enzymes
- Alzheimer probes
  (for amyloid protein and neurofibrillary tangles)
- Translocator Protein Ligands
[\textsuperscript{11}C]L-Deprenyl Labels Monoamine Oxidase B

Smokers have low MAO\textsubscript{B} activity

Fowler et al., 1996
Alzheimer’s Disease

$[^{18}\text{F}]$FDG Shows *Deficits in Temporal-Parietal and Frontal Areas*

Jagust et al., 2010
FDDNP binds to neurofibrillary tangles and amyloid plaques. Binding is negatively related to cognitive performance.

Braskie et al., 2010
[¹¹C]PIB and [¹⁸F]FDDNP

- [¹¹C]Pittsburgh Compound B (PIB) labels amyloid plaque deposition (red).
- [¹⁸F]FDDNP labels plaques and tangles — binding in regions of high tangle accumulation (green).

Colors indicate binding in AD subjects minus binding in Control subjects. 

Shin et al., 2010
Hot Topic

ET imaging of Neuroinflammation

Number of publications

Year

‘Microglia and PET’ (1094)
Translocator Protein (TSPO): Target of neuroinflammation PET tracers
Neuroinflammation in Methamphetamine Users Measured with $^{11}$C(R)-PK11195
Animal Models

**MicroPET**

- 30 detector modules (8x8)
- 1920 individual LSO elements
- ring diameter 17.2 cm
- 10 cm transaxial FOV
- 1.8 cm axial FOV
- volume resolution ~ 6 µL
- sensitivity: 210 cps/µCi
Fig. 1. (a) Mockup of the RatCAP ring on the head of a rat. (b) Ratturn bowl used to support ring and allow freedom of movement.

Fig. 4. Block detectors form a ring connected with a flexible cable that serves as bus for transmitting serial data of the ring and receiving power and control signals.
PET scans of a rat's brain made with the RatCAP scanner (horizontal view superimposed on a rat brain atlas figure, left, and a coronal slice, right). The rainbow scale (red = high, violet = low) indicates the level of a radiotracer that binds to receptors for dopamine, which are concentrated in the striatum, a brain region involved in reward and motivation.
PET fMRI Multimodality Imaging
Striatal D2-type Dopamine Receptors and Complex Decision-Making

The Balloon Analogue Risk Task
Striatal D2-type Dopamine Receptors and Complex Decision-Making

The Balloon Analogue Risk Task

Total $0.75

Total $0.00
Parametric Modulation of Activation by Pump Number

Parametric analysis to test linear relationship between pump number and brain activation
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Parametric analysis to test linear relationship between pump number and brain activation.

Nonparametric regressors to control for mean activation with each event.
Frontostriatal Activity is Modulated by Risk and Reward

Pumping an active balloon (whole-brain Z-statistic map)  

Cashing Out (whole-brain Z-statistic map)

M. Kohno et al., Cerebral Cortex, 2013
**Striatal Dopamine Receptors and Risk-Taking**

Cortical Activity is Modulated by Risk

Modulation is Related to Dopamine Receptors in Striatum

\[ r = -0.770 \]

M. Kohno et al., Cerebral Cortex, 2013
Stopping Associated with Activation in PFC-Pre-SMA-Subthalamic Nucleus Network

A Aron, R Poldrack: J Neurosci, 2006
DA D2/D3 Receptor Availability is Related to Stopping Ability

R

Caudate
SSRT (msec)
300
260
220
180
140

Putamen
SSRT (msec)
300
260
220
180
140

DA D$_2$/D$_3$ Receptor Availability (BP$_{ND}$)

$[^{18}F]$Fallypride PET

Healthy Control Participants

D Ghahremani et al., 2012

R

p$<.1$  p$<.02$

p$<.1$  p$<.02$
Caudate DA D2/D3 Receptor Availability is Related to Fronto-striatal fMRI Response during Inhibition

fMRI - $[^{18}\text{F}]$Fallypride PET

Healthy Control Participants

Caudate Stop vs. Go parameter estimates

$R = 0.82$

D Ghahremani et al., 2012
Cortical DA release during inhibition on the SST

Whole-brain voxel-wise paired t-test comparing BPND between baseline “Go” and SST scan conditions (n = 9). The “hot” colorscale indicates voxels where BPND, BL was significantly higher than BPND, SS (increased DA during SST). Display threshold p < 0.005, uncorrected, k > 10.

DS Albrecht et al., Synapse, 2014
Why do PET instead of another technique?

Molecular resolution

Specific biochemical processes (metabolic, enzymatic)

Neurotransmitter function

Pharmacological agents interacting in situ
Advantages of PET over fMRI:

*For functional imaging:* When blood flow is not a marker for neuronal activity (e.g., when a drug has direct effects on microvasculature)
- Deoxyglucose method (FDG) – insensitive to changes in blood flow.
- When fMRI is not possible – implanted stimulators

*For assay of specific neurotransmitter systems:*
- Can label tracers with C-11, F-18 -- Chemical flexibility.
- High sensitivity
  Assay of receptor binding requires ability to detect nM or pM concentrations.
Advantages of fMRI over PET:

**Time resolution:**
PET has a 10-minute window for repeat measurements with [O-15]water.
fMRI has temporal resolution beyond tens of milliseconds

**Spatial resolution:**
~2 mm for hi-res scanner (HRRT)
No need for ionizing radiation with fMRI.
Summary

Molecular neuroimaging with PET:
• Functional studies avoiding confound of direct vascular effects
• Neurotransmitter-specific probes
• Also enzymes and other metabolic markers
• Static and dynamic measures
• Animal studies possible
• Can be paired with fMRI – in multi-modality imaging.