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# Psychiatric Applications of Positron Emission Tomography of the Brain

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# What is positron emission tomography (PET)?

- PET is the imaging of physiology in vivo.
- PET is a non-invasive technique that uses positron-labeled tracers (radioactive isotopes) to specific biological molecules to map the activity and distribution of these substances in human tissues in order to localize and quantitate metabolic and physiologic activity in the organ of interest.
- PET has revolutionized the study of neurobiology, neurochemistry, and neuropharmacology and is becoming an invaluable tool in psychiatric research.



## How does PET work?

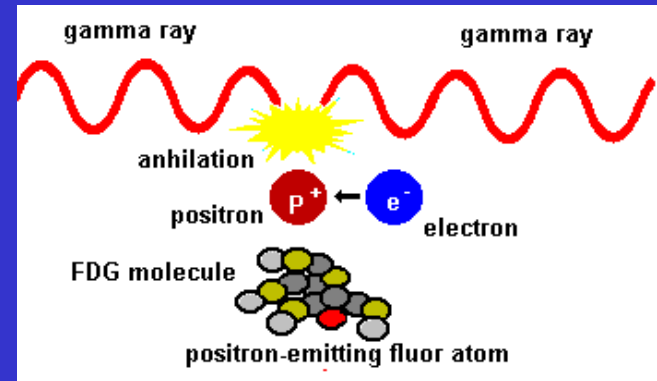
- Each patient is injected with a small amount of the radioactive ligand and placed into the PET scanner
- PET uses radiation emitted from the patient to develop images
- A variety of compounds have been labeled with radioactive ligands that are positron emitting isotopes
- Compounds are chosen based on their biologic availability and activity in the region of interest
- As the radioactive ligands undergo radioactive decay, their nuclei emit positrons



## How does PET work, continued?

- As each positron is released, it collides with an electron and produces two gamma rays of the same energy traveling in different directions

- These gamma rays leave the body and are detected by a gamma detector camera in the PET scanner



<http://www.epub.org.br>

- Inside the gantry the radiation detectors emit a pulse of light each time they are hit by a gamma ray

- A photomultiplier amplifies the pulse of light, the information is processed by a computer, and an image of the brain is reconstructed

- The computer evaluates both the location and the number of radioactive pulses emitted by the brain in order to generate a reconstruction that shows both the location and concentration of the radioactive ligand, creating a map of brain activity



# How is brain activity measured?

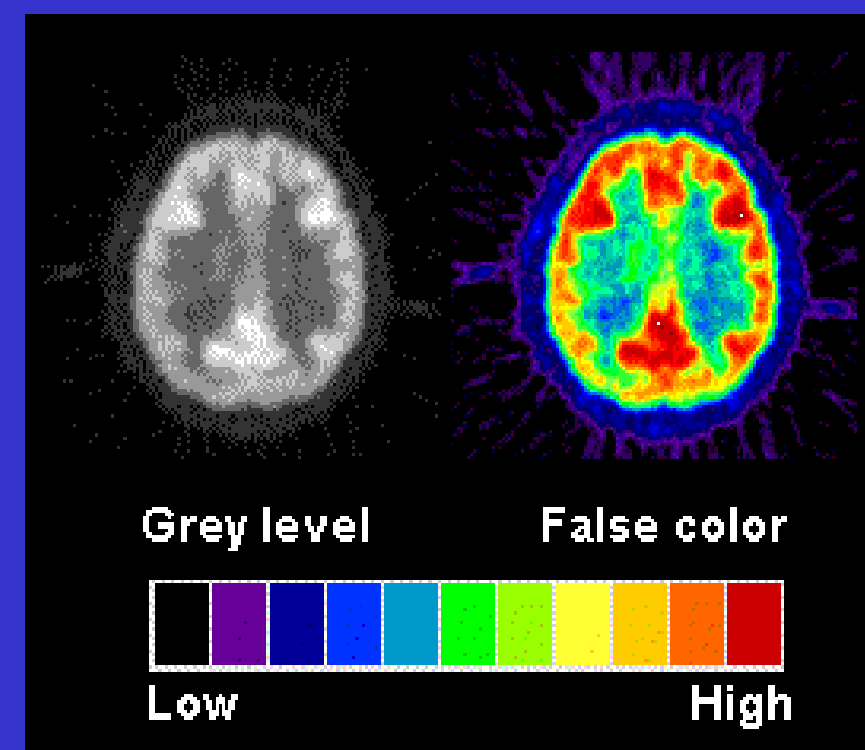
Various shades of gray, called **gray levels**, correspond to the intensity of the signal recorded.

**Black** = Zero counts, no activity

**White** = Multiple counts,  
most activity

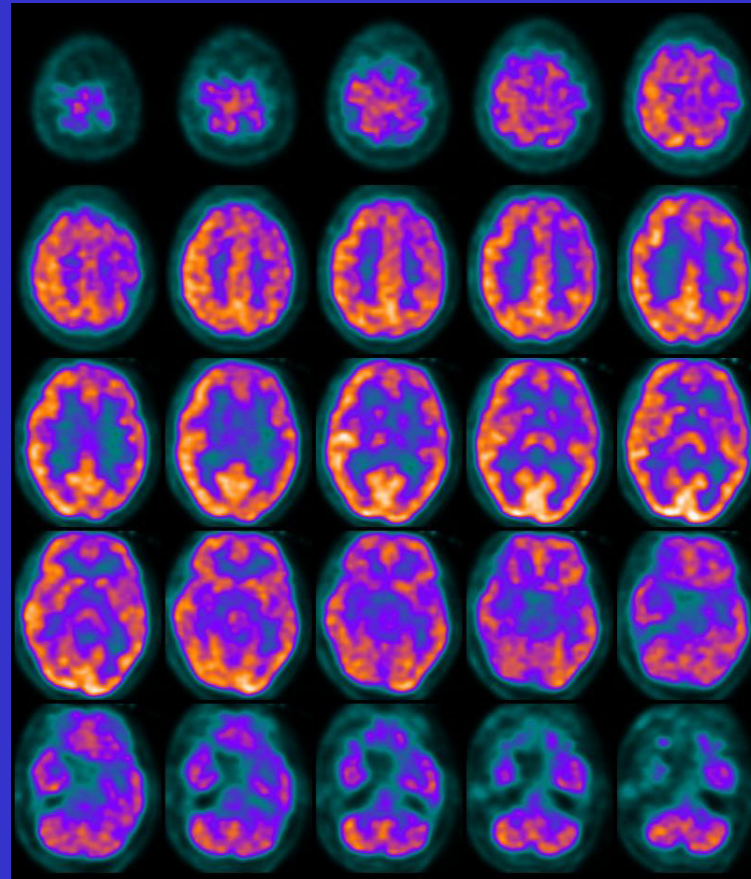
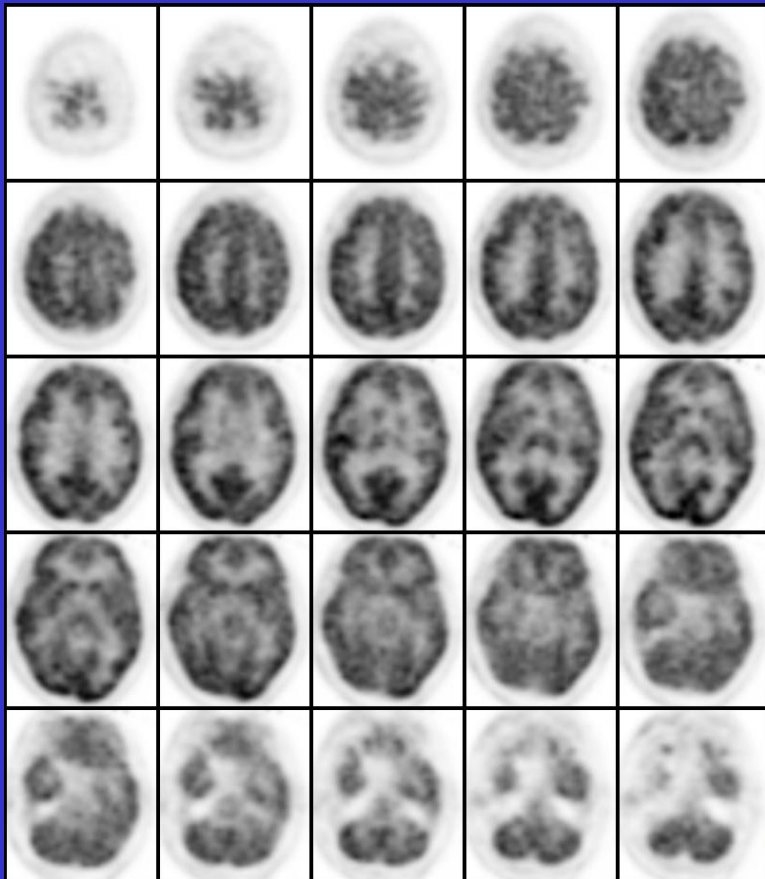
The images can also be viewed using the **false color** scale in order to more easily visualize the most active regions

Axial, coronal, and transverse sections can be viewed





# Axial brain images on PET scan



courtesy of Kevin Donohoe, MD, BIDMC



# What is single photon emission computed tomography (SPECT)?

- SPECT is a functional imaging technique very similar to PET.
- Both PET and SPECT are isotope-based techniques that use the same principle and technology to elaborate the physiology of the brain
- The main practical difference between PET and SPECT is that the isotopes used for SPECT emit only one single photon/gamma ray, not two.
- These single photon emitting isotopes have longer half lives and consequently can be used for prolonged studies of drug-receptor occupancy.



# PET vs SPECT

PET	SPECT
More sensitivity	Sensitivity improving
More resolution ( $2 \times$ SPECT), e.g. 4.5 mm FWHM	Resolution improving (7.0–12.0 mm FWHM)
More expensive	Less expensive
Small study samples (expensive)	Larger study samples (lower cost)
Short-half-life isotopes (20 min)	Longer half-life isotopes (e.g. $^{123}\text{I}$ –13 h)
Fewer centres can afford the technology and expertise required: on-site cyclotron needed	Ease of use (ligands radio-labelled without loss of radiological activity)

Data from Bailey *et al*, 1994; Kerwin *et al*, 1994c.  
FWHM, full width half-maximum.

Bigliani V, Pilowsky LS. In vivo neuropharmacology of schizophrenia. *British J Psych* 1999; 174 (38S): 23-33.





# Radiolabelled ligands used in neurology and psychiatry

Function	Ligand
Blood flow/perfusion	<sup>99m</sup> Tc-hexametazime (hexamethylpropylene-amine-oxime, HMPAO) <sup>99m</sup> Tc-ethylcysteine dimer (ECD)
Blood-brain barrier	<sup>99m</sup> Tc-pertechnetate
GABA/benzodiazepine receptor	<sup>123</sup> I-iomazenil
Postsynaptic D <sub>2</sub> receptor	<sup>123</sup> I-benzamide (IBZM)
Presynaptic dopamine transporter	<sup>123</sup> I-fluoropropyl carboxymetoxynortropane (FP-CIT)
5-HT <sub>2</sub> receptor marker	<sup>123</sup> I-SB 207710
Potassium analogue	<sup>201</sup> Tl (thallium chloride)
Tumour markers	<sup>99m</sup> Tc-MIBI, <sup>99m</sup> Tc-tetrofosmin <sup>123</sup> I-α-methyltyrosine
Glucose metabolism	<sup>18</sup> F-fluorodeoxyglucose (FDG)
Cellular proliferation	<sup>18</sup> F-fluorothymidine
Dopamine decarboxylase marker	<sup>18</sup> F-levodopa
Aminoacid metabolism	<sup>14</sup> C-methionine

Costa DC, Pilowsky LS, Ell PJ. Nuclear medicine in neurology and psychiatry. *Lancet* 1999; 354:1107-1111.



# What processes can PET evaluate?

The targeting of specific molecules:

- Receptors
- Transporters
- Enzymes
- Neurotransmitters

Allows the study and quantification of basic cerebral processes and functioning signals, for example:

- Cellular metabolism (glucose, oxygen, amino acids)
- Blood flow and blood volume
- Protein synthesis
- Receptor-ligand binding (neurotransmitters, drugs, etc)
- Integrity of the blood-brain barrier



# How is PET used clinically?

Diagnosis

Acute stroke

Early Assessment

Brain trauma

Management

Brain death

Prognosis

Epilepsy

Dementia & Depression

Parkinson's disease

Brain tumors



# What role does PET play in psychiatry?

- 1) Measurement of glucose uptake
- 2) Measurement of cerebral blood flow (CBF)
- 3) Neuroreceptor mapping
- 4) Drug development



# 1) Measurement of glucose uptake

- Glucose metabolism in the brain fuels the energy requirements of ion pumps and the neurotransmitter recycling systems.
- Regional changes in the utilization of glucose in the brain reflect differences in neuronal activity.
- Two major types of studies have been derived from this principle:
  - A) Studies of the brain at rest or while conducting some neuro-psychiatric attentional task
  - B) Studies of the brain when challenged pharmacologically, affectively or cognitively



## 2) Measurement of cerebral blood flow

- Cerebral blood flow, like glucose utilization, is another marker for neuronal activity in the brain.
- Cerebral blood flow is also used as an outcome measure for challenge studies.
- Specific patterns of reduced cerebral blood flow have been found to correlate with some psychiatric conditions.

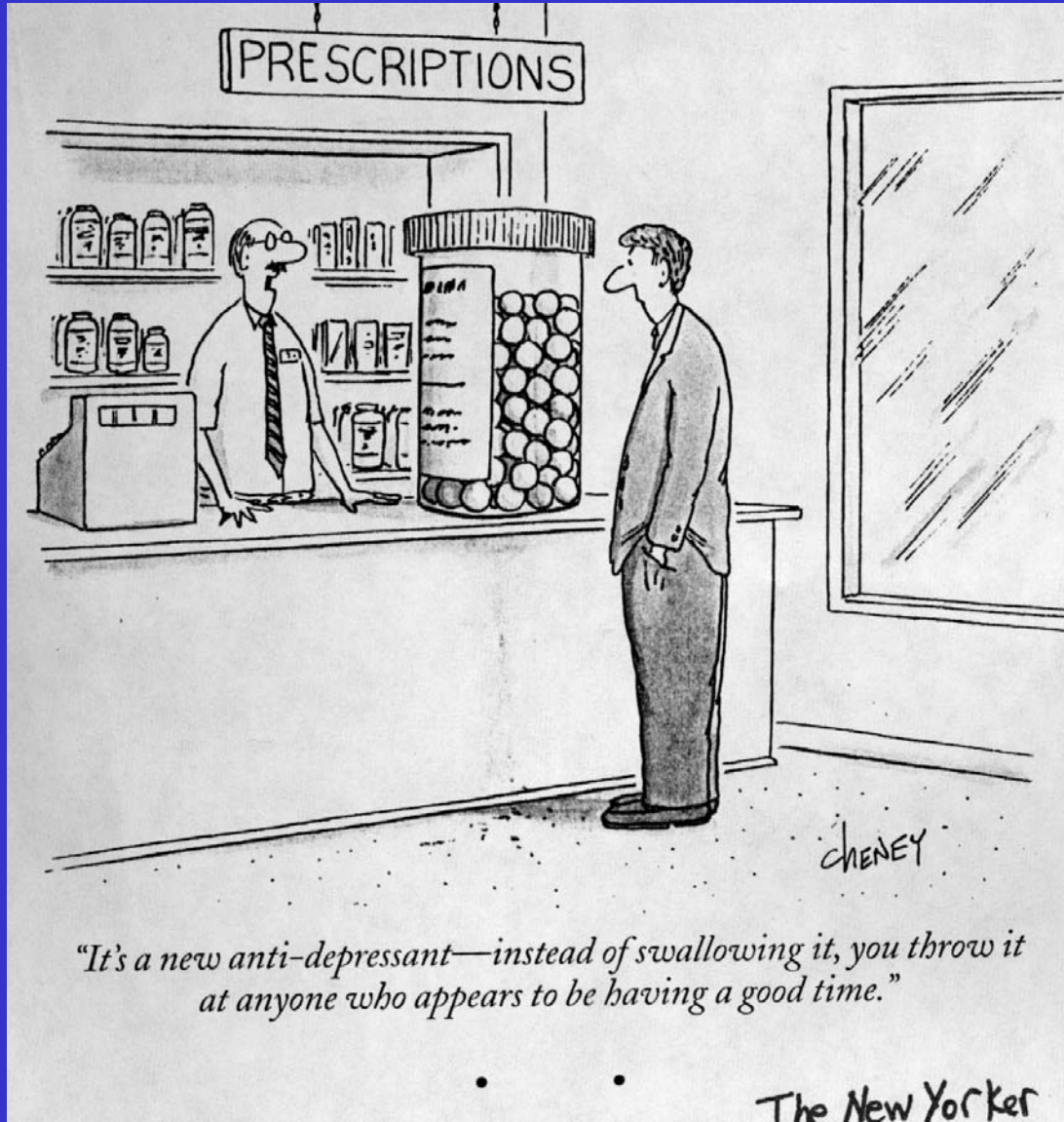


### 3) Neuroreceptor mapping

- Allows the investigation of neurotransmitter activity and the identification of abnormalities in neurotransmission in the brains of patients with psychiatric illness.
- Allows the quantification of absolute numbers of receptors for specific ligands as well as the evaluation of the concentration of receptor activity in various regions of the brain.
- Allows the characterization of abnormal patterns of neurotransmission and receptor distribution specific to each psychiatric illness that may ultimately aid in diagnosis by generating characteristic patterns of abnormalities that correlate with specific psychiatric diseases.
- Is a fundamental tool in the evaluation of psychotropic drugs.



## 4) Drug Development







## 4) Drug development, continued

- Much of our understanding of psychiatric illness is a by-product of the response of patients to various psychiatric medications.
- PET imaging of the brain reveals the precise relationship between psychotropic drugs and receptors and offers detailed information on pharmacokinetics.
- Using PET, investigators can answer questions about each drug, like:
  - Does it cross the blood-brain barrier?
  - What is its specific receptor target?
  - How long does it occupy its receptor?
  - What neurochemical factors predict good response?
  - What is a therapeutic dose?

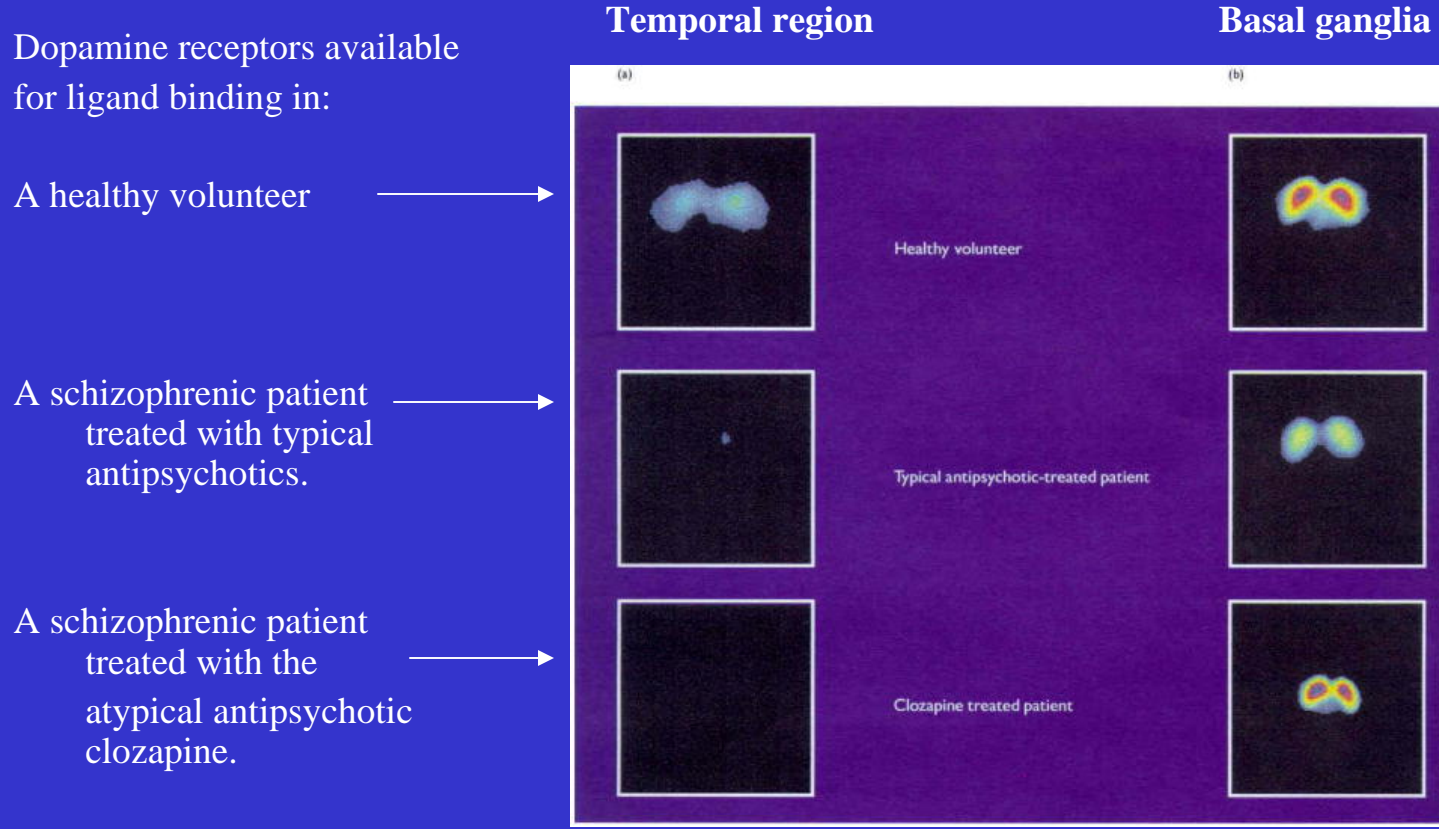


# Case presentation: Schizophrenia

- The dopamine hypothesis of schizophrenia states that schizophrenics have increased activity of mesolimbic dopamine systems.
- This hypothesis is based on the following experimental observations:
  - 1) D2 receptor blockade is the primary requirement for effective antipsychotic medication
  - 2) Post-mortem studies have shown elevated levels of D2 receptors in the brains of schizophrenic patients
- PET scanning has allowed for more detailed examination of the dopamine hypothesis of schizophrenia.



# Imaging of the brain in schizophrenia: Dopamine receptor occupancy



Bigliani V, Pilowsky LS. In vivo neuropharmacology of schizophrenia. *British J Psych* 1999; 174 (38S): 23-33.

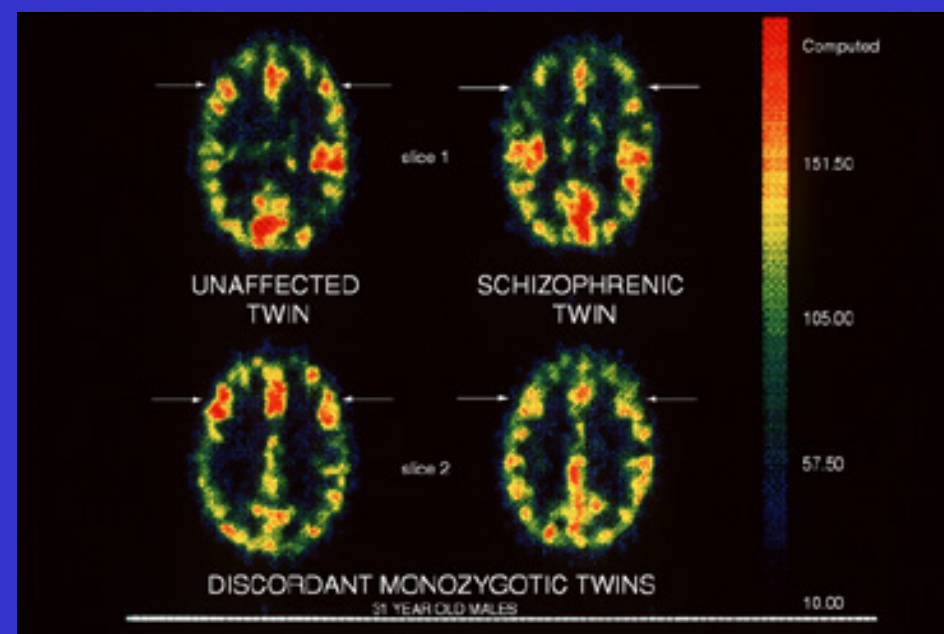


# Imaging of the brain in schizophrenia: Cerebral blood flow

The frontal lobe of the brain is responsible for higher cognitive thought processes.

This PET scan is from a study of monozygotic twins discordant for schizophrenia.

The twins with schizophrenia have reduced brain activity in the frontal lobe as compared to their unaffected twin when evaluated during a card sorting test.



Berman KF, Torrey EF, Daniel DG, Weinberger DR.  
[www.nimh.nih.gov/hotschi/scanschi.htm](http://www.nimh.nih.gov/hotschi/scanschi.htm)



## Future directions of PET in psychiatry

- Improvement of existing PET and SPECT technology in order to generate images with better resolution
- Development of new radioligands to evaluate other relevant receptor sites
- Substantiation of existing data with larger, well-designed study protocols and further post-mortem examinations of brain tissue
- Integration of PET scanning into mainstream clinical psychiatric practice



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