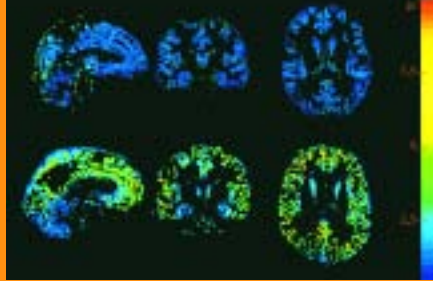
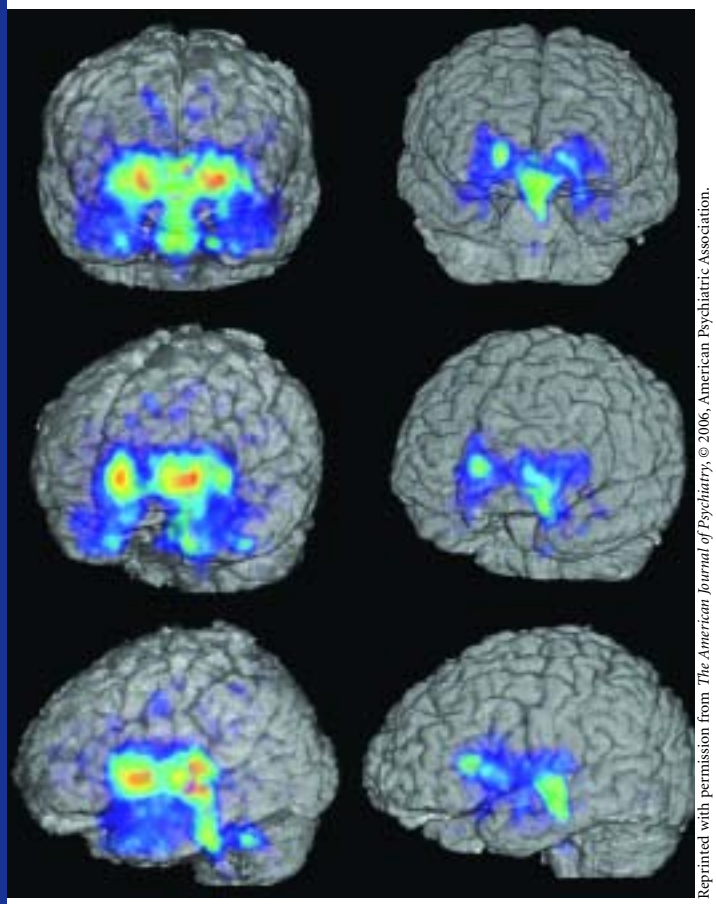
Visualizing Mental Illness:
Using PET to improve diagnosis and treatment



The science of diagnosing and treating psychiatric illnesses has always depended heavily on clinical judgment. Even administering psychiatric medication – a relatively direct process in most physical illnesses – is rarely guided by laboratory tests. A patient's improvement is judged clinically, and sometimes patients and doctors have different perceptions of benefit. For some drugs, it can take weeks or months to determine effectiveness, and determining optimal dosages may require numerous attempts. For patients with severe disorders, even one week can be too long to wait for improvement.

Now, two clinical studies using positron emission tomography (PET) to track biomarkers of psychiatric illnesses may remove some of the guesswork. These studies, based on the measurement of brain chemicals, have the potential to improve diagnosis and treatment of a host of psychiatric diseases. "A biomarker is a physical trait that can be measured biologically, such as a specific chemical in the blood or DNA," says **Ramin V. Parsey, MD, PhD,** *Assistant Professor of Clinical Psychiatry* at NewYork-Presbyterian Hospital/ Columbia University Medical Center. "By using PET to view biomarkers such as beta amyloid and serotonin, it is possible to track the progression of disease and the response to treatment."



Reprinted with permission from *The American Journal of Psychiatry*, © 2006, American Psychiatric Association.

PET scans of a healthy volunteer (left panel) and a depressed patient (right panel). Increased concentrations of red indicate the presence of more serotonin transporters in the healthy patient than in the depressed patient.

PET scans can reveal the state of the brain at the level of the neurotransmitters by viewing how chemicals in the brain rise or fall in association with the progression of psychiatric illnesses. Examples include beta amyloid, which accumulates in the brain as Alzheimer's disease progresses, and serotonin, levels of which are abnormal in the brains of people with major depression and bipolar disorder, or manic depression.

Study 1: **Understanding Alzheimer's Disease**

In one study of elderly patients, researchers at the Columbia Kreitchman PET Center are investigating how much beta amyloid is present in the brain during the early stage of Alzheimer's disease. Using PET, they are comparing brain images of people with normal memory, people with mild cognitive impairment but not Alzheimer's disease, and people with early, mild Alzheimer's disease. "Measuring beta amyloid may allow physicians to detect Alzheimer's disease much earlier – before patients develop memory deficits," explains **J. John Mann, MD,** *Professor of Radiology and Psychiatry* at Columbia University College of Physicians and Surgeons. This study will then provide a baseline for a second stage of research on drugs used to reduce levels of beta amyloid in patients with Alzheimer's disease.

PET can also help physicians monitor how well drugs work by measuring their impact on biomarkers, instead of waiting for patients to develop debilitating symptoms such as memory loss. "Sometimes drugs work by preventing a problem such as memory loss from getting worse, rather than helping it to get better. Examining the level of beta amyloid in the brain can provide a more sensitive biomarker of whether the drug is working well," says Dr. Mann.

Study 2: **Major Depression**

Using the PET scanner in genetic studies, Dr. Mann and Dr. Parsey seek to understand the role of specific genes in the development of major depressive

Top: a normal brain; Bottom: the brain of an Alzheimer's patient showing increased presence of beta amyloid.

illness, and determine whether specific treatments may work for people according to their genetic makeup.

Current treatment for depression includes a range of antidepressant medications, each of which may need to be taken for 4 to 8 weeks before its effects on an individual can be determined. If one medication doesn't work, the patient must then try another. "But for a depressed person, even a week feels like forever," states Dr. Mann. Moreover, untreated major depression is the main cause of suicide. "With suicide the third leading cause of death among young people and the 11th leading cause of death in the U.S. in adults, the treatment of depression is a very important thing." Now, results from PET scans may help predict which patients will respond to which antidepressant drugs.

In this study, the team uses PET scans in combination with a panel of genetic tests from blood samples to gather data from participants. Patients in the study receive comprehensive evaluations and drug treatment at no cost.

Evaluations of depressed or bipolar patients, or even patients who have had an episode of depression in the past but are currently feeling well, include:

- PET scans of the serotonin system in the brain,
- MRI (while patients are off medication), and
- Measurements of key genes in the serotonin system.

"Sensitivity to stress can be measured by the level of expression of the serotonin transporter gene. People who have low levels of expression of this gene and are exposed to adversity are more likely to suffer depression than people who have higher levels," says Dr. Mann. The researchers have found that certain changes on the PET scan and specific serotonin gene variants predict who will recover with treatment. However, they are still establishing which combinations of genes and serotonin PET scans are the best predictors. "In time," Dr. Mann predicts, "we expect these scans and lab tests to become part of clinical practice."

Looking to the future, Dr. Mann suggests that, because it can show how much of a drug is needed to bind to specific targets, "this new use of PET also has the potential to accelerate the development of new drug treatments." PET scanning can determine the lowest dose of medications required to act on the targets of their action in the brain. This can help physicians determine the dose range required for optimal benefit and the fewest side effects, Dr. Mann explains. "Before PET was available, we had to do dose-finding clinical studies. Not only did they take a great deal of time, but they followed the principle of determining the maximum dosage of the drug that could be tolerated without troublesome side effects. Now we can use PET to determine the least amount of drug to be effective and avoid a lot of side effects."

The use of PET may help researchers to:

- **Detect disease before symptoms occur.**
- **Predict how patients will respond to particular therapies.**
- **Speed the development of new drugs.**

Drs. Mann, Parsey, Oquendo, and colleagues have developed methods using Positron Emission Tomography (PET) for visualizing how the brain responds to serotonin. These techniques allow further study of mood disorders and the effects of treatment. Some of these studies include:

- **Neurobiology of Depression and Antidepressants,** funded by National Institutes of Mental Health, $3 million. Dr. Mann, Principal Investigator.
- **Familial Pathways to Early-Onset Suicide Attempts,** funded by National Institutes of Mental Health, $2.5 million. Dr. Mann, Principal Investigator.
- **Psychobiological Predictors of Suicidal Behavior in MDE (Major Depressive Episodes),** funded by National Institutes of Mental Health, $1 million. Dr. Mann, Principal Investigator.
- **Biological Predictors of Treatment Response,** funded by the National Institutes of Health, $2.7 million. Dr. Parsey, Principal Investigator.
- **Imaging of Serotonin Transporters in Depression,** funded by National Institutes of Mental Health, $1 million. Dr. Parsey, Principal Investigator.

For referrals or more information, please contact Drs. Mann, Parsey, or Oquendo: 212.543.6774.