Translational Imaging

1. Highlights

The Division of Translational Imaging continues to be the largest PET user in the Medical Center, accounting alone for more than 50% of research PET scans performed in the last year in the PET Kreitchman Center. In addition, MRS and fmri research, are more routinely performed to complement the information obtained with PET.

2. Staff

Division Chief, Anissa Abi-Dargham, MD, Psychiatrist Research II, Grade 38
Lawrence Kegeles, MD, PhD, Research Scientist 6, Grade 35
Mark Slifstein, PhD, Research Scientist 6, Grade 35
Anna Xu, PhD, Research Associate

3. Overview

The area of research of the Division of Translational Imaging (DTI) at NYSPI is the development of novel tools and techniques to study neurotransmission in the living human brain, and the application of these techniques to clinical studies to unravel chemical imbalances associated with severe mental illnesses and drug addiction. Molecular imaging techniques based on Positron Emission Tomography (PET) are the main methods developed and used in the Division. The imaging approach has a translational emphasis, using imaging to identify phenotypes that can be tested in animal models or vice versa using models derived from preclinical knowledge to be tested in clinical populations.

Development of new imaging techniques include design of new radiotracers (organic synthesis, chemical structure-activity relationship, in vitro evaluation, experiments in rodents and primates, dosimetry and toxicology evaluation, filing of IND, phase 1 and 2 studies in humans), as well as development of new imaging paradigms based on pharmacological challenges, cognitive tasks or electromagnetic challenges to measure responsivity of neurotransmitter systems.

Clinical investigations within the Division focus on schizophrenia, cannabis dependence and comorbidity with schizophrenia, MDMA dependence, design of paradigms to assess dopamine release in response to alcohol challenge and reward related tasks, identification of biomarkers for disease prevention or drug discovery and aid in drug development. Additionally, the Division performs imaging studies in collaboration with other investigators who specialize in the study of various disorders: anxiety disorders (Dr. Simpson), mood disorders (Dr. Schneier), autism (Dr. Hollander from Mt Sinai), personality disorders (Dr. Siever from Mt Sinai) and alcoholism (Dr. Krystal from Yale).

4. Current Research

Imaging

Cortical D1 Imaging: Scans with [11C]SCH23390 and [11C]NNC112, two tracers for the D1 receptor, will be obtained in a sample of patients with schizophrenia and their matched controls. This will address the discrepant findings obtained with these two tracers in schizophrenia.

Striatal and extrastriatal D2 function:

Studies in healthy controls to assess extrastriatal release of dopamine using the high affinity [18F]fallypride are now completed and show that reliable signal is obtained in important extrastriatal regions such as the amygdala, hippocampus, thalamus and substantia nigra.

Studies with the high affinity [18F]fallypride tracer combined with the amphetamine challenge will inform us about the status of dopamine release in extrastriatal regions in schizophrenia and replicate the findings within the substructures of the striatum. We are also assessing with microdialysis in monkeys the correspondence between the PET measured DA release and actual intrasynaptic increase.

[18F]Fdopa studies in prodromal patients in collaboration with the COPE clinic aim at predicting conversion using [18F]Fdopa uptake in the striatum as an indicator of who will convert to schizophrenia.
Imaging gene effects on receptors in the brain: this is an ongoing effort, with collection of DNA on all subjects who undergo imaging.

Treatment research
Atomoxetine challenge in patients with schizophrenia and controls with COMT val/val alleles and cognitive testing is underway to test the effects of NET inhibition on improving cortical dopamine transmission and related cognitive functions.

A D1 agonist clinical trial funded by NIMH (PI: J. Lieberman) will start this coming year. IND pending. This will provide a proof of concept for cognitive enhancement in schizophrenia with subacute administration of a D1 agonist. PET occupancy will be measured in humans and in non human primates.

MRS research
High-field MRS studies with the 3T GE MR system are conducted in patients with schizophrenia to study GABA and glutamate function in the dorsolateral prefrontal cortex (DLPFC). In addition in collaboration with Dr. Lisanby, the responses of these transmitters to acute administration of rTMS to the DLPFC are evaluated.

Prodromal subjects from COPE clinic are assessed with MRS measures of GABA and glutamate function to compare with the same MRS measures in patients with schizophrenia.

In collaboration with the TURNS multicenter study of cognition in schizophrenia (Dr. Lieberman, PI), patients participating in a trial of a GABAergic agonist for cognitive enhancement receive MRS evaluations of GABA and glutamate function before and during study medication administration.

Alcoholism Research
We previously reported a regionally selective decrease in amphetamine induced DA release in the ventral striatum in recently detoxified alcohol dependent subjects compared to controls measured with high resolution Positron Emission Tomography (PET) and $[^{11}C]$raclopride. D2 receptor density was decreased in all striatal substructures and was related to daily drinking prior to abstinence. Whether these alterations are a vulnerability factor to develop alcoholism, or a consequence of chronic alcohol exposure is unclear. We have now undertaken a series of studies aiming first at developing paradigms to assess dopamine release as sensitive probes for vulnerability, and at applying these paradigms in young at risk healthy volunteers to compare FHN and FHP subjects matched for drinking habits. These studies are funded by the Center for Translational Neuroscience of Alcoholism.

5. Education and Training
The Division also trains fellows in the acquisition of the expertise and skills required for clinical investigation using PET, with focus on basic receptology, neurochemistry, pharmacology and pharmacokinetics, in depth teaching of PET imaging, functional neuroanatomy, kinetic analysis on a region or voxel based approach, as well as general principles of clinical investigation (CGMP, statistics, drafting of IRB protocols).

Current fellows are: Nina Urban, MD, and Judy Thomson, PhD

6. Awards and Honors
NIDA R01, PI: Anissa Abi-Dargham: four-year, $1.9 million, for PET imaging studies of dopamine transmission in cannabis dependence. This study will, for the first time, yield information on the effects of chronic cannabis use on the dopaminergic-related reward circuits in the brains of human subjects, allowing meaningful comparisons between cannabis, a drug thought by many to be harmless, and other drugs such as cocaine and alcohol.
7. Publications

Papers


Schneier FR, Martinez D, Abi-Dargham A, Zea-Ponce Y, Simpson HB, Liebowitz MR, Laruelle M. (2007) Striatal dopamine D(2) receptor availability in OCD with and without comorbid social anxiety disorder: preliminary findings. *Depress Anxiety*


Books

Abi-Dargham and Guillen (2007) Integrating the Neurobiology of schizophrenia. *Int Rev Neurobiol* 78